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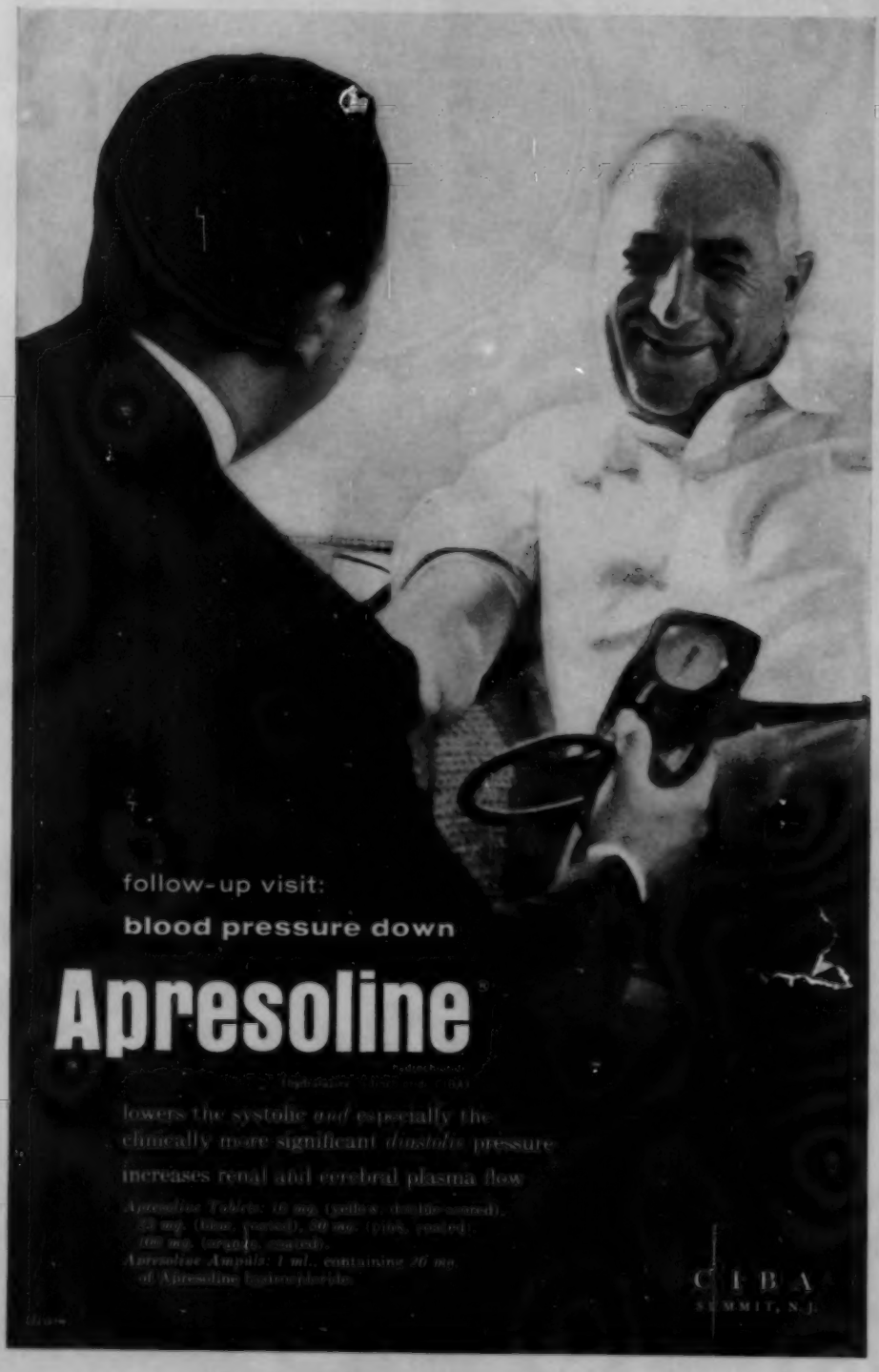
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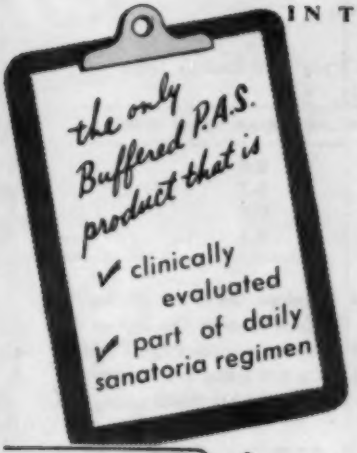

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BLOOD CONCENTRATION STUDIES WITH BUFFERED PARA-AMINOSALICYLIC ACID TABLETS

The ability of para-aminosalicylic acid (PAS) to delay the emergence of strains of tubercle bacilli resistant to other antituberculous drugs used concurrently with PAS makes it a valuable drug in the treatment of tuberculosis. This advantage is lost when the drug is discontinued or reduced in dosage because of drug intolerance of the patient. In many cases these unfavorable reactions take the form of gastrointestinal upsets such as nausea, vomiting, and diarrhea caused by drug irritation.

Buffered PAS tablets[1] are reported to be better tolerated than other currently used PAS preparations.[2] This tolerance is said to be due to the unique buffer[3] incorporated into each tablet, which reduces or prevents gastrointestinal upset.

The therapeutic efficacy of PAS tablets is not determined by tolerance alone, however, but by the attainment of adequate blood concentrations. Therefore, a study was undertaken to compare blood concentrations attained with buffered PAS tablets against those obtained with the more commonly used sodium PAS solution.

The method used for determining PAS blood concentrations is one developed in this laboratory[4] and gives results similar to those obtained by the procedure of Klyne and Newhouse.[5] It is based upon the formation of a yellow color produced by the addition of a solution of 3-methoxy-4-hydroxybenzaldehyde to a solution of PAS. The intensity of the color is proportional to the concentration of PAS in solution. The determination is performed upon protein-free blood plasma filtrates obtained by precipitating proteins with 20 per cent trichloracetic acid and by subsequent centrifugation and filtration. A portion of the filtrate is reacted with 3-methoxy-4-hydroxybenzaldehyde and the pH adjusted with sulfuric acid. The color intensity is then read spectrophotometrically and the reading compared with a previously constructed standard graph.

In order to determine blood concentrations following administration of buffered PAS tablets and of sodium PAS solution, three groups of either 5 or 6 patients each were chosen and, after discontinuation of medication for a thirty-six-hour period, each group was given the particular form and dosage of PAS to be determined. Two blood samples were taken from each patient at different hours and more than 150 determinations were performed.

Comparison of PAS blood concentrations which were reached following single doses of buffered PAS tablets and sodium PAS solution are shown in tables 1 and 2. In tables 3, 4, and 5 may be seen individual and average concentrations after multiple dosage with the two forms of PAS. The figures illustrate graphically, for rapid comparison, the averages of the individual results obtained with similar regimens of both buffered PAS tablets and sodium PAS solution.

* * *

There is general agreement among investigators that a concentration of 1.5 mg. of PAS in 100 ml. of plasma is bacteriostatic for tubercle bacilli, and that 2 mg. per 100

[1] A product of Panray Corporation, New York, New York.

[2] BRONX VETERANS ADMINISTRATION HOSPITAL: Quarterly Progress Report of the Veterans Administration-Army-Navy Study on the Chemotherapy of Tuberculosis, April, 1953, p. 14.

[3] The tablets consist of 0.5 gm. of PAS buffered with dihydroxy aluminum amino-acetate and calcium carbonate.

[4] DEEB, E. N., AND VITAGLIANO, G. R.: J. Am. Pharm. A. (Scient. Ed.), 1954, *44*, 182.

[5] KLYNE, W., AND NEWHOUSE, J. P.: Lancet, 1948, *2*, 611.

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TABLE 1

PAS Blood Plasma Concentrations Following Single 4 Gm. Dose of Buffered PAS Tablets

1 hour	2 hours	3 hours	4 hours	6 hours	8 hours
Blood Concentration in Mg. per 100 Ml.					
5.7	6.4	1.7	2.3	2.6	0.6
5.7	1.3	5.6	3.7	4.4	0.9
2.5	6.1	3.7	2.5	4.0	1.7
1.1	3.5	6.1	4.0	1.4	0.6
3.2	4.0	2.7	4.0	1.7	3.6
1.6	1.7	5.1	3.5	1.5	1.9
Average of the Above Levels					
3.3	3.8	4.2	3.3	2.6	1.6

TABLE 2

PAS Blood Plasma Concentrations Following Single 5.5 Gm. Dose of Sodium PAS Solution*

1 hour	2 hours	3 hours	4 hours	6 hours	8 hours
Blood Concentration in Mg. per 100 Ml.					
8.8	6.2	4.0	5.0	0.7	0.3
8.6	7.0	3.8	2.2	1.3	0.5
9.5	6.2	2.8	5.3	0.5	0.1
12.5	4.8	3.8	3.2	0.5	0.3
10.5	6.2	6.6	3.1	1.0	0.5
Average of Above Levels					
10.0	6.1	4.2	3.8	0.8	0.3

* Five and one-half gm. of sodium PAS are equivalent to 4 gm. of PAS.

TABLE 3

PAS Blood Plasma Concentrations Following Multiple Dosage with Buffered PAS Tablets

4 Gm. Three Times Daily*

1 hour	2 hours	3 hours	4 hours	6 hours	8 hours
Blood Concentration in Mg. per 100 Ml.					
8.3	6.8	7.2	5.1	4.6	4.0
9.5	10.2	8.4	5.1	4.4	2.9
12.8	8.0	7.6	3.5	5.1	4.6
9.5	7.2	6.6	3.7	4.0	2.5
7.7	9.8	4.6	3.4	1.9	0.9
Average of Above Levels					
9.6	8.4	6.9	4.2	4.0	3.0

* Samples taken after second dose of the day.

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TABLE 4

PAS Blood Plasma Concentrations Following Multiple Dosage Therapy with Sodium PAS Solution

A Dose Equal to 4 Gm. PAS Was Given Three Times Daily*

1 hour	2 hours	3 hours	4 hours	6 hours	8 hours
Blood Concentrations in Mg. per 100 Ml.					
11.4	6.8	2.9	4.2	0.7	0.3
11.0	4.2	3.1	1.3	0.5	0.3
12.5	7.7	4.9	2.9	1.4	1.0
9.5	7.7	4.9	2.5	2.0	0.7
11.0	4.6	3.7	1.0	1.3	0.5
Average of Above Levels					
11.1	6.2	3.9	2.4	1.2	0.6

* Samples taken after second dose of the day.

TABLE 5

PAS Blood Plasma Concentrations Following Multiple Dosage with Buffered PAS Tablets

2 Gm. Three Times Daily*

1 hour	2 hours	3 hours	4 hours	6 hours	8 hours
Blood Concentration in Mg. per 100 Ml.					
2.2	3.0	4.0	1.4	4.0	2.5
3.3	2.4	3.7	4.6	0.7	0.5
2.9	4.4	4.4	1.7	1.7	1.3
4.5	3.7	2.9	4.9	1.4	0.9
3.6	3.1	3.3	3.7	2.0	1.4
Average of Above Levels					
3.3	3.3	3.7	3.3	2.0	1.3

* Samples taken after second dose of the day.

ml. or more is an adequate therapeutic concentration.[6] Determinations in this laboratory indicate that comparatively high blood concentrations are obtained in the first two hours after administration of sodium PAS solution. However, much higher concentrations are maintained for a longer period of time, after the first two hours, by administration of a single 4 gm. dose of buffered PAS tablets than with an equal dose of sodium PAS solution (tables 1 and 2). Therefore it appears that, if given in equal doses, blood concentrations obtained with buffered PAS tablets compare most favorably with blood concentrations found in patients who have received sodium PAS solution. This becomes more evident when, after multiple-dose therapy with equal doses of buffered PAS tablets and sodium PAS solution, the blood concentrations produced after the fourth hour by the administration of buffered PAS tablets are found to be approximately three times higher than those obtained with sodium PAS solution (tables 3 and 4).

[6] Nilson, H.: Tubercle, 1953, *34*, 100.

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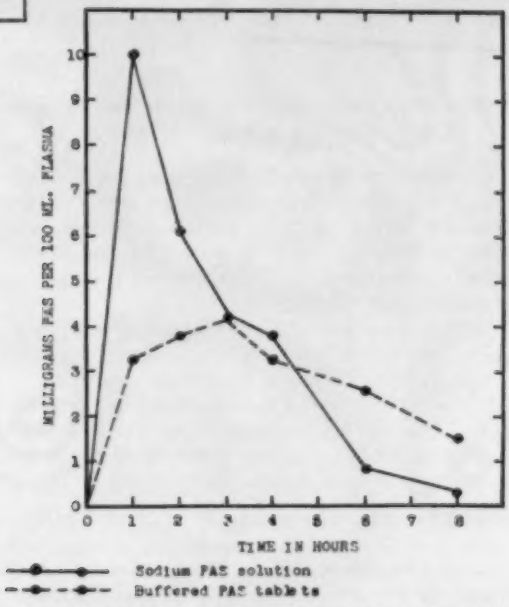

FIG. 1. Comparison of blood concentrations following single doses of sodium PAS solution and buffered PAS tablets. Each dose is equivalent to 4 gm. of para-aminosalicylic acid.

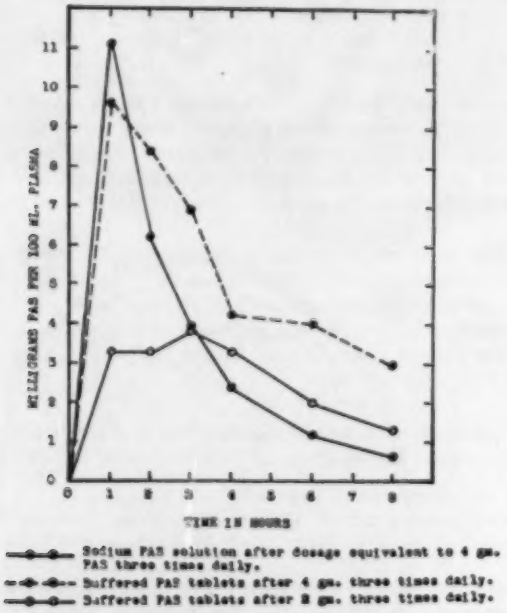

FIG. 2. Comparison of blood concentrations found following multiple-dose therapy with different types and dosages of PAS. Therapy was interrupted to permit blood sampling at the time intervals indicated in figure 1.

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TABLE 1

PAS Blood Plasma Concentrations Following Single 4 Gm. Dose of Buffered PAS Tablets

1 hour	2 hours	3 hours	4 hours	6 hours	8 hours
Blood Concentration in Mg. per 100 Ml.					
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5.7	1.3	5.6	3.7	4.4	0.9
2.5	6.1	3.7	2.5	4.0	1.7
1.1	3.5	6.1	4.0	1.4	0.6
3.2	4.0	2.7	4.0	1.7	3.6
1.6	1.7	5.1	3.5	1.5	1.9
Average of the Above Levels					
3.3	3.8	4.2	3.3	2.6	1.6

TABLE 2

PAS Blood Plasma Concentrations Following Single 5.5 Gm. Dose of Sodium PAS Solution*

1 hour	2 hours	3 hours	4 hours	6 hours	8 hours
Blood Concentration in Mg. per 100 Ml.					
8.8	6.2	4.0	5.0	0.7	0.3
8.6	7.0	3.8	2.2	1.3	0.5
9.5	6.2	2.8	5.3	0.5	0.1
12.5	4.8	3.8	3.2	0.5	0.3
10.5	6.2	6.6	3.1	1.0	0.5
Average of Above Levels					
10.0	6.1	4.2	3.8	0.8	0.3

* Five and one-half gm. of sodium PAS are equivalent to 4 gm. of PAS.

TABLE 3

PAS Blood Plasma Concentrations Following Multiple Dosage with Buffered PAS Tablets

4 Gm. Three Times Daily*

1 hour	2 hours	3 hours	4 hours	6 hours	8 hours
Blood Concentration in Mg. per 100 Ml.					
8.3	6.8	7.2	5.1	4.6	4.0
9.5	10.2	8.4	5.1	4.4	2.9
12.8	8.0	7.6	3.5	5.1	4.6
9.5	7.2	6.6	3.7	4.0	2.5
7.7	9.8	4.6	3.4	1.9	0.9
Average of Above Levels					
9.6	8.4	6.9	4.2	4.0	3.0

* Samples taken after second dose of the day.

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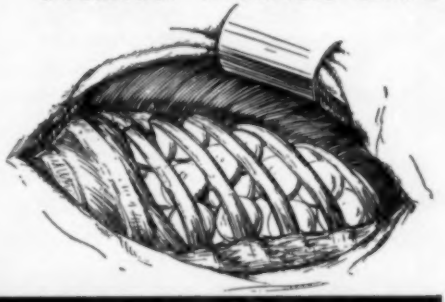

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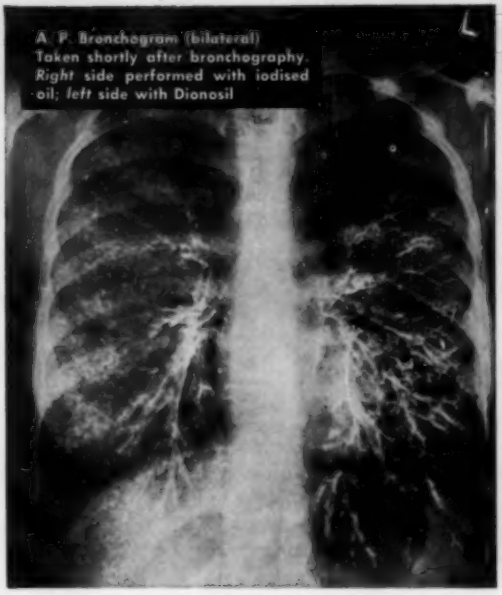
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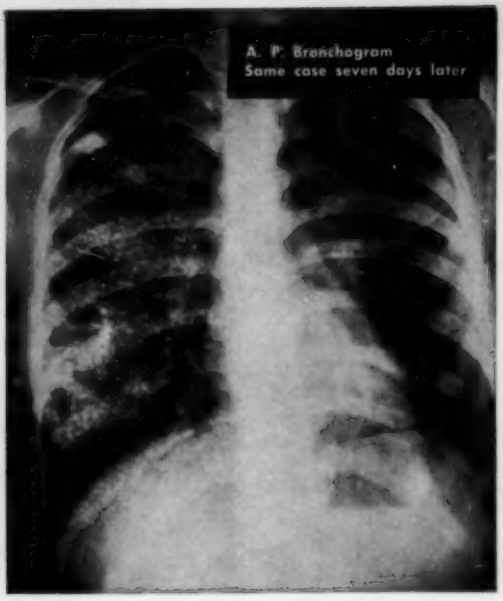

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THIRD ANNUAL SYMPOSIUM ON ANTIBIOTICS

Washington, D. C., November 2, 3 and 4, 1955

by 1. Shubin, H., and Heiken, C. A.
2. Morton, R. F.; LeCaillie, R. A.; Gold, A., and Prigot, A.
3. Payne, H. M.; McKnight, H. V., and Harden, K. A.

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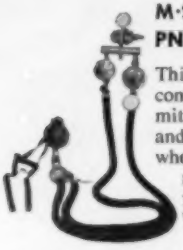

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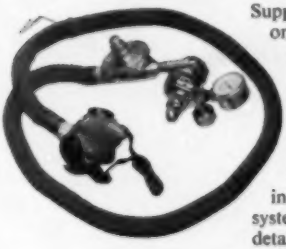

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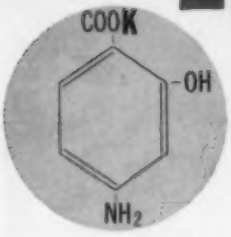

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1. *Molthan, L., Cohen, R. V., and Zarafonetis, C. J. D.: Clinical use of potassium para-aminosalicylate (KPAS). Am. Rev. of Tuberc. and Pulmon. Dis. 71:220 (Feb.) 1955.*

2. *Cohen, R. V., Molthan, L., and Zarafonetis, C. J. D.: Clinical Studies of Various Forms of PAS (with special reference to plasma concentrations). Read before the American Trudeau Society, Annual Meeting, Milwaukee, Wisconsin, May 23-27, 1955.*

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REFERENCES:

1. Camarata, S. J.; Jacobs, H. J., and Affeldt, J. E.: Read Before The Southern California Chapter of The American College of Surgeons, Palm Springs, Calif., January 23, 1953.
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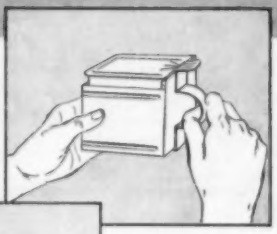

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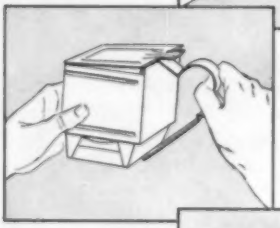

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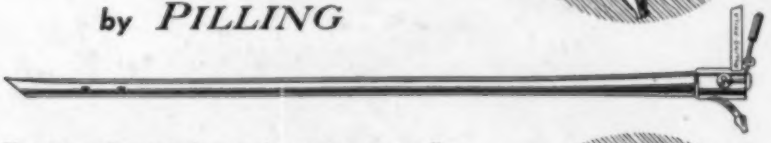

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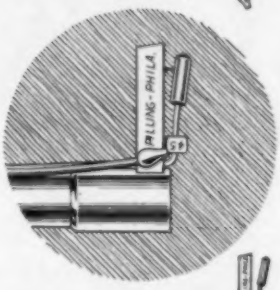

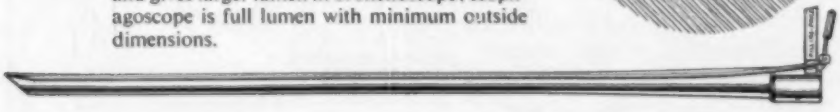

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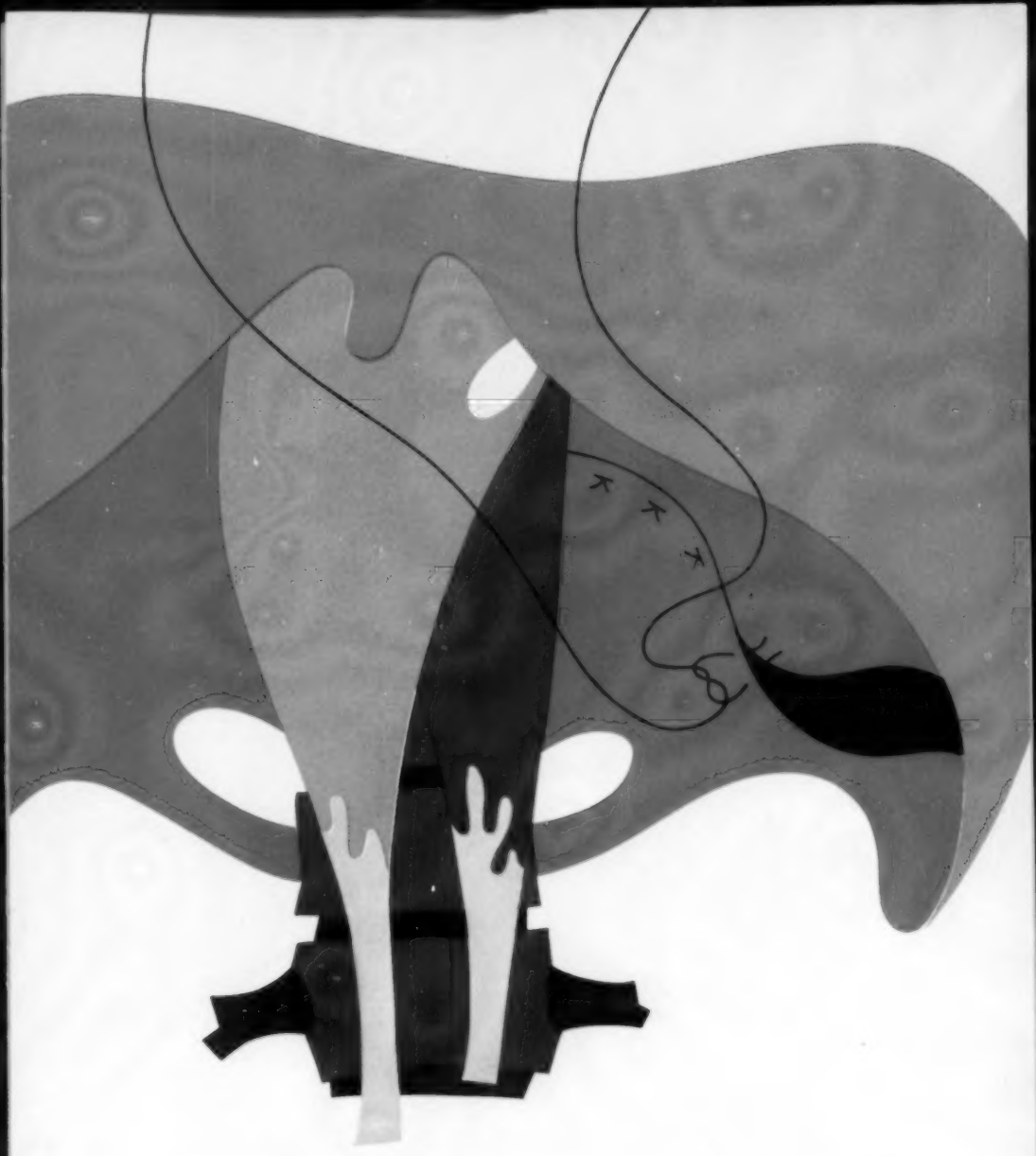

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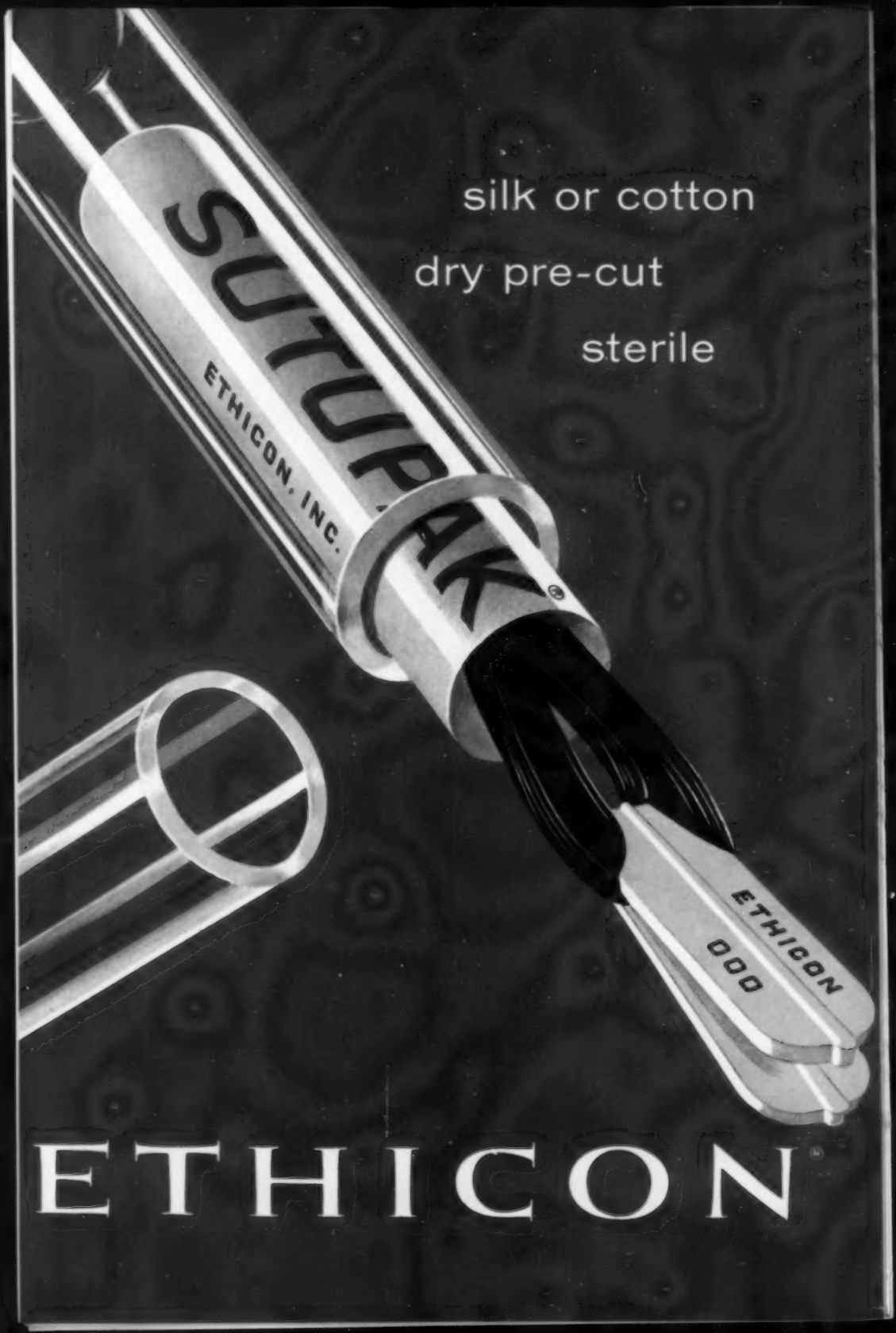
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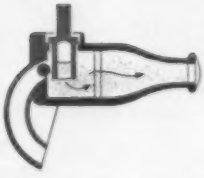

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A Laboratory and Clinical Report on Adrenosem® Salicylate

(BRAND OF CARBAZOCHROME SALICYLATE)

History

The first investigation of a hemostat with an action comparable to Adrenosem Salicylate was made by Derouaux and Roskam[1] in 1937. They reported that an oxidation product of adrenalin, adrenochrome (which has no sympathomimetic properties), has prompt hemostatic activity.

It was further found that various combinations of adrenochrome, notably the oxime and semicarbazone, produced stable solutions. But, these were so slightly soluble that sufficient concentration could not be obtained for practical therapeutic use. By combining these adrenochrome compounds in a sodium salicylate complex a stable, soluble form can be obtained. This complex has been given the generic name, carbazochrome salicylate, and is supplied under the trade name Adrenosem Salicylate.

Roskam, in his study entitled "The Arrest of Bleeding,"[2] enumerates "the drugs whose efficaciousness as hemostatics have been proved by accurate methods in experimental animals and in healthy men as well. . . . One is the monosemicarbazone of adrenochrome [Adrenosem Salicylate]."

Chemistry

Adrenosem Salicylate is a synthetic chemical. The full chemical name is adrenochrome monosemicarbazone sodium salicylate complex.

Pharmacology

Although it is chemically related to epinephrine, Adrenosem Salicylate has no sympathomimetic effects. It does not alter blood components, nor does it affect blood pressure or cardiac rate.[2-7]

(* U.S. Patent 2,581,850)

Sherber, in an early study,[3] concludes that Adrenosem Salicylate* "is a potent antihemorrhagic factor in those conditions in which the integrity of the smaller vessels is interrupted, and is superior to any similar material that is now available."

He continues, "From our experience it appears that adrenochromazone complex is indicated in preventing vascular accidents incident to hypertension; in maintaining small vessel integrity; in the preoperative preparation where oozing from a vascular bed is anticipated, as in tonsillectomies, adenoidectomies and prostatectomies; and as an adjunct in the treatment of bleeding from such surgical procedures."

Adrenosem Salicylate may be administered simultaneously (but separately) with any type of anesthetic, anticoagulant, or vitamin K and heparin.

A Unique Systemic Hemostat

Clinical investigators[2-7] are in agreement that Adrenosem Salicylate controls bleeding and oozing by decreasing capillary permeability and by promoting the retraction of severed capillary ends. It aids in maintaining normal capillary integrity by direct action on the intercellular "cement" in capillary walls. The interesting work of Fulton[8] confirms this. Adrenosem Salicylate, since it is not a vasoconstrictor, has no effect on large severed blood vessels and arterioles.

Adrenosem Salicylate is being used both prophylactically and therapeutically in thousands of hospitals, and in virtually every type of surgical procedure. It has also proved most useful in dental surgery.[7]

Owings reported on the use of Adrenosem Salicylate in controlling postoperative adenoid bleeding in 102 cases.[4] "We have used 2½ mg.

(½ ampule) intramuscularly, 15 minutes before anesthesia for children and 5 mg. (1 ampule) for adults." In only one patient did bleeding occur. Three others showed red blood from the nose and mouth. These patients "were then given 5 mg. intramuscularly, with prompt and complete control. We have also noticed that bleeding stopped more promptly on the operating table."

This is a 1% incidence of postoperative bleeding using Adrenosem Salicylate preoperatively, compared to an incidence of 10% postoperative bleeding in all cases taken from previous records, without Adrenosem Salicylate medication.

Peele reports on the use of Adrenosem Salicylate in treating 178 patients with 24 different conditions.[5] The drug was first used to control postoperative hemorrhage from the adenoid region. He adds: "The results were so dramatic that since that date [1953] Adrenosem Salicylate has been used postoperatively to reduce bleeding from all otolaryngologic and bronchoesophagolic procedures, to treat postoperative hemorrhage from the tonsil and adenoid regions, and to treat selected cases of epistaxis."

The effectiveness of Adrenosem Salicylate in controlling bleeding and oozing in 330 patients is reviewed by Bacala.[6] "Our experience of the effect of carbazochrome salicylate on 317 surgical indications and 13 obstetricogynecological conditions, has been therapeutically encouraging and successful for the control of capillary bleeding. Foremost among the cases studied were 223 tonsillectomies definitely benefited by this metabolic hemostat, making a diminution of the control incidence of posttonsillectomy bleeding of 19.8% down to 7%. It has also been found useful in gastro-intestinal bleeding, cataract extraction, epistaxis, incisional seepage, trans-urethral prostatectomy, menometrorrhagias, cervical ooze, antepartum and postpartum bleeding, threatened abortion, and prevention of capillary hemorrhages during hedulin or dicumerol therapy."

Side Effects

All investigators concur that, at recommended dosage levels, Adrenosem Salicylate is free from toxic effects. No cumulative effects attributable to the drug have been reported.

The only side reaction noted has been a transient stinging sensation in the area of injection when Adrenosem Salicylate is used intramuscularly. As one investigator comments: "The brief discomfort which attends the injection of Adrenosem into the gluteal region has not been a significant problem in children or adults as originally anticipated."[5]

Indications

Idiopathic purpura, retinal hemorrhage, familial telangiectasia, epistaxis, hemoptysis, hematuria.

Postoperative bleeding associated with:
tonsillectomy, adenoidectomy and nasopharynx surgery;
prostatic and bladder surgery;
uterine bleeding;
postpartum hemorrhage;
dental surgery;
chest surgery and chronic pulmonary bleeding.

Dosage

For recommended dosage schedules, please send for detailed literature.

Supplied

Ampuls: 5 mg., 1 cc. (package of 5).
Tablets: 1 mg. S.C. Orange, bottles of 50.
Tablets: 2.5 mg. S.C. Yellow, bottles of 50.
Syrup: 2.5 mg. per 5 cc. (1 tsp.), 4 ounce bottles.

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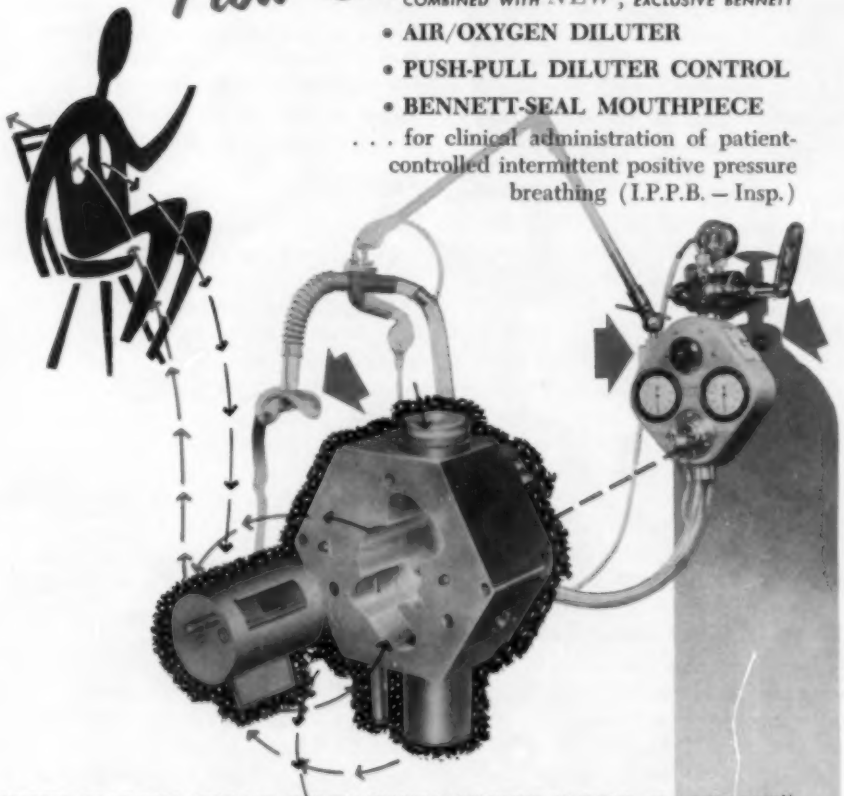

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DISEASES of the CHEST

VOLUME XXIX FEBRUARY, 1956 NUMBER 2

The Pathology and Bacteriology of Resected Lesions in Pulmonary Tuberculosis***

HENRY C. SWEANY, M.D., F.C.C.P.†
Mt. Vernon, Missouri
and
HAWLEY H. SEILER, M.D., F.C.C.P.‡
Tampa, Florida

The advances in surgery of pulmonary tuberculosis combined with proper rest and antimicrobic therapy have revolutionized practically every phase of the tuberculous problem. Among others, bacteriological changes have been phenomenal. Great differences have been recorded in microscopic findings, resistance to antimicrobial agents and virulence for experimental animals. Changes in the primary etiologic agent have correspondingly led to many radical variations in pathology. Less has been written about pathology, but not until surgical resection became proficient was there enough material for complete study. Newer methods of treatment have reduced deaths from tuberculosis and along with the reduction in deaths, there has been a corresponding reduction in bodies for autopsy study. On the other hand, there has been created a wealth of material from surgical resection that has opened new fields for study, not only in bacteriology, but more especially in pathology of the disease. Rapid clearing of infiltrative lesions, encapsulation of tubercles and shrinking of cavities have already been noted and the end is not in sight. Certainly nobody will feel that we are near the end of new discoveries.

Medlar, Bernstein and Steward[1] reported on significant bacteriological changes in resected lesions. They found that all open cavities had acid fast bacilli, but only 13 per cent of "closed" lesions had acid fast bacilli. Closed lesions included "filled in" cavities or necrotic lesions that had not sloughed. They found practically no "secondary" bacteria, in spite of the fact that the caseous walls of many cavities contained a preponderance of neutrophiles. The conclusion was that tubercle bacilli, in addition to secondary microorganisms may be responsible for the neutrophiles. The same authors also found that a few specimens contained

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many acid fast bacilli that fail to produce tuberculosis in guinea pigs.

Beck and Yegian[2] found acid fast bacilli in cases not treated with antibiotics that did not grow on cultured media. They concluded that sluggish or inactive forms may be from natural causes, as well as from cases having had drug treatment.

Steenken and Wolinsky[3] observed low virulence in one case not having drug therapy, but in a series of 21 on isoniazid therapy, they were able to show that 14 strains of bacilli lost virulence completely. Nine strains from seven cases were fully virulent. Six of the nine virulent strains were fully resistant to isoniazid. They concluded that there was no relation in the loss of virulence to either time of exposure to isoniazid or to its *in vitro* resistance. In cultures they were able to cause a total loss of virulence of (H 37 RV) by transfers of bacilli in increasing concentrations of isoniazid. As to recovery of bacilli from resected pulmonary lesions, Bernstein and Steenken[4] were unable to grow bacilli from 12 "target point" lesions with positive bacilli on smear and only one culture of five lesions where no bacilli were found on smear. In "non target point" lesions they were able to grow cultures and infect guinea pigs in about two-thirds of the cultures. "Albumen homogenates" yielded little better results than saline solution in preparing specimens.

In a round table discussion by a group at the Los Angeles Meeting of the National Tuberculosis Association in 1953[5] there was much debate, but not much agreement regarding the viability of the "sleepers" that have been reported by various authors. It was agreed that better culture methods may produce more growths. All were agreed that the lesions were sterilized but not all that the bacilli were dead. Dubos[6, 7] on several occasions offered valid reasons why we could not consider the bacilli dead until more refined methods are used. He suggested the effect of tissue acids especially lactic acid and spermine, as well as toxic substances on the ability of tubercle bacilli to grow. He also mentioned the possibility of exhaustion of a vital metabolite that must be restored before growth and reproduction can take place.

As to the pathologic changes, much less has been reported.

There are many different manifestations of healing that range all the way from a clearing of infiltrates, resorption of small tubercles; encapsulation, calcification and ossification of larger ones; closing of bronchi with collapse and healing of the cavity by fibrosis or inspissation of fluid and pus, which after long intervals may become sterile, caseate and actually calcify. Of these many changes, the most spectacular is the healing of cavities.

It is not our purpose to give a detailed history of healing cavities which were first described by Laennec. Before the antibiotic era, several references were made to healing cavities. Gilbert[8] described two cases where cavities were healed by scar tissue and Sweany[9] discussed and described several types of cavity closure. The complete closure of a bronchus may lead to a collapse of the cavity wall, and the cavity may close by scar tissue. In the event the cavity wall is too rigid or is held out by

adhesions, pus, and other fluids may be trapped in the cavity. Another type is the healing from within by a gradual shrinking of the cavity and a building up of a healing fibrous layer in a centripetal manner until the lumen becomes essentially closed. Still another is the pressure of organized pleural fluid on the cavity wall sometimes resulting in closure. An example of complete healing of a cavity by scar tissue following collapse by pneumothorax was shown. Auerbach and Green[10] described cavity healing in a group of sputum-negative cases. There was one case followed by ante-mortem roentgenograms which healed by scar tissue. The pathological changes were minutely detailed in the healing process. They further described what they called "closed healing" with "inspissation of the caseous contents." In contrast to "open healing" where the bronchus remains open and the cavity gradually closes by the ingrowth of fibrous tissue and with sometimes a partial covering by epithelial cells growing out from the bronchial stem. Pinner[11] showed practically the same type of material but rightly took exception to calling the closure of a cavity by inspissation an anatomically healed lesion. He admitted error, however, in his earlier contention that closure of the bronchi played no role in healing.

There are many other isolated references to natural cavity closure, but for the present purpose only certain well-documented reports are given.

After antibiotic therapy, followed by surgical resection, there are several important reports on the healing of resected lesions, most of which deal with clearing of infiltrations, resorption of cellular exudates, fibrous contractions of lesions, and partial closure of cavities with a great variety of healing manifestations. Auerbach, Katz and Small[12] described several resected specimens where there was partial and even almost complete closure of cavities with fibrosis, granulation tissue and clearing of caseation, and "pyogenic membranes." They laid great emphasis on re-epithelialization beginning at the broncho-cavitary junction and extending out into the cavity wall for varying distances depending on the chronicity of the process. They state that antibiotic therapy tends to keep the bronchus open in contrast to the closure that usually occurs without antibiotics. Altman and Ornstein[13] presented similar material in a series of resected specimens.

Ryan, Medlar and Welles[14] reported on the pathological changes in resected lesions and described "reversible" and "inreversible" pneumonias. The former cleared leaving the tissues practically intact, while the latter caused caseation that either excavated or became encapsulated. Some cavities became compressed into smaller sizes.

Schmidtmann and Liebaldt[15] also examined the pathological changes that took place in resected specimens. They demonstrated closing of bronchi by ingrowths of granulation tissue. Also they showed that bronchi become compressed from without until only a compact mass of epithelium remains.

The study to be reported has to do chiefly with some of the pathologic changes that take place following antimicrobial therapy in tuberculosis.

TABLE I
ANALYSIS OF 34 CASES HAVING PULMONARY SURGERY

CODE:
I. & K.—infiltrates and cavity
tpy.—thoracoplasty
Sm. & C.—smear and culture
atel.—atelectasis
decort.—decortication
tub.—tubercle
Pn.—pneumonectomy
pnp.—pneumoperitoneum
arr.—arrested
fibr.—fibrosis
cas.—caseous
sthzd.—streptohydrazid

No.	Initial	Case Number	Race	Age	Sex	Onset Date	Predominant Sympt. of Onset	Admission Diagnosis		Treatment
1	I.A.	3572	W	24	F	2/52	Cough, chills & fever	8/9/53	F.A. Act.	Sm. PAS. INAH, 10/52 to present
2	W.W.	3053	C	39	F	10/51	Pleuritis	4/15/52	F.A. Act.	Sm. 6/52 to 9/53; PAS 6/52 to 8/53
3	R.B.	1582	W	42	F	1/49	Cough, Wt. Loss night sweats	3/24/49	F.A. Act.	Pnp. 4/49 to 5/53; Sm. 8/49 to 8/53; INAH 8/52 to 10/53; Sthzd. 8/52 to 10/53
4	C.H.	2091	C	38	M	3/49	Cough, Wt. Loss night sweats	1/25/50	F.A. Act.	Sm. & PAS. 1/50 to 10/53
5	M.B.L.	2050	C	19	F	10/49	Laryngeal	12/27/49	M.A. Act.	Pnp. 10/49 to 5/52; Sm. 8/50 to 2/54; PAS. 8/50 to 12/53; INAH 8/52 to 12/53
6	J.B.	3350	W	55	M	12/50	Cough, Wt. Loss weakness	12/52	F.A. Act.	Sm. 10/53 to 12/53; Sthzd. 1/52 to 10/53
7	H.L.	1551	W	29	F	1/49		3/49 4/51 1/54	M.A. Act.	Sm. PAS. Pnp. irregular for 4 years, Adm. 3 times
8	N.L.	3415	W	42	F	2/53	Hemorrhage	2/18/53	M.A. Act.	Sm. PAS. INAH 2/53 to 1/54
9	M.P.	2599	W	28	F	'51	Insidious	3/20/51 3/20/52	F.A. Act.	Pnp. 4/51 to 2/53; Pnx. 10/51 to 10/52; Sm. PAS. INAH from '52 to 1/54
10	T.L.Y.	3107	C	27	M	1/52	Laryng. Wt. Loss, N.S.	5/4/52	F.A. Act.	Sm. & INAH 5/52 to 10/53
11	C.W.	3280	W	29	M	9/52	Cough, Wt. Loss	10/4/52	M.A. Act.	Pnx. 7/53 to 1/54; Sm. & INAH 10/52 to 1/54
12	D.D.	3548	W	22	M	'50	Cough, Wt. Loss	7/22/53	M.A. Act.	Various drugs in four hospitals, a committed patient at operation time
13	D.V.W.	3447	W	27	F	3/52	Cough, Wt. Loss Weakness	3/17/53	F.A. Act.	Sm. PAS. & INAH 3/53 to 3/54
14	M.G.	3003	C	48	M	1/52	Cough, Laryng.	3/12/52	F.A. Act.	Sm. PAS 4/52 to 1/54
15	C.G.	2383	C	44	M	5/50	Cough, Wt. Loss	8/30/50	F.A. Act.	Sm. & PAS. 9/50 to 12/53; Sthzd, 12/52; INAH 7/52 to 12/53

16	W.R.	2950	C	42	M	3 Adms.		1/17/53	M.A. Act.	PAS. & INAH 1/53 to 10/53
17	W.C.B.	2605	W	38	M	2 Adms.		1/18/53	F.A. Act.	Sthzd. c. PAS. & INAH alt. days from 8/53 to 3/54
18	F.H.	3615	C	29	F	5/52	Cough, Wt. Loss Malaise	10/10/53	M.A. Act.	INAH 5/52 to 3/54; PAS. 10/53 to 3/54
19	E.B.	2586	W	37	F	7/53	Cough, Wt. Loss	8/53	M.A. Act.	Pnx. 8/50 to 7/52; Sm. 18 injections in '51
20	W.J.	3192	W	17	F	5/52	Cough, Wt. Loss Weakness, N.S.	8/19/53	F.A. Act.	Sm. PAS. INAH 8/52 to 3/54
21	D.S.	3760	W	21	F	9/53	Cough, Wt. Loss Malaise	2/10/54	F.A.Q.	Sm. and PAS. 9/53 to 3/54
22	E.S.	2107	C	30	F	12/48	Pl. Fever, N.S. Cough	2/9/50	F.A. Act.	Sm. & PAS. 3/50 intermit. 4 yrs. INAH 8/52 to 3/20/54
23	M.C.	3529	W	17	F	'53	"Mobile X-ray"	7/7/53	M.A. Act.	Sm. & PAS. 7/53; Sm. discont. 4/54 INAH 4/54
24	R.F.	3286	W	20	F	6/53	Cough, fever, Wt. Loss	10/15/52	F.A. Act.	Sm. PAS. & INAH intermittent from 11/52 to 4/54. Pnp. 2/52 to 8/53
25	G.R.	3304	C	38	M	2/51	"Routine X-ray"	11/19/52	M.A. Act.	PAS. & INAH 12/53 to 3/54; Sm. 3/53 to 3/54
26	W.B.	3530	W	42	M	5/53	Cough, Wt. Loss	7/7/53	F.A. Act.	Sm. PAS. INAH 7/53 to 3/54
27	L.F.	1534	W	30	M	Before '49		1/49 3/19/53	F.A. Act.	Many courses Sm. & PAS. 4 yrs. in different hospitals INAH, PAS., '53 to '54
28	L.W.	3135	C	28	M	'51	Productive Cough, Hem., Wt. Loss, Night Sweats	'51 6/52	F.A. Act.	Pnp. 12/52 to 2/54; Sm. & PAS. 6/52 to 2/54; INAH 9/52 to 2/54
29	S.C.	3239	W	39	M	'52		1/54	F.A. Act.	Drugs in other hospitals—INAH & PAS. 1/54 to 4/54
30	K.J.	379	C	43	F	5/47	"X-ray"	10/5/52	F.A. Act.	Sm. & PAS in other hospitals; Sm. PAS. INAH 10/52 to 1/54
31	H.M.	3567	W	39	M	'49	Cough and Hemorrhage	8/19/53	F.A. Act.	Tpy. other hospital, also other drugs Sthzd. PAS. INAH 12/53 to 5/54
32	L.O.	2689	W	59	M	'50	Cough, Weakness	5/21/51	F.A. Act.	Sm. PAS. INAH 12/53 to 5/54
33	E.W.	3373	W	23	F	'49	Cough, Hem. Fatigue, N.S.	1/13/53	F.A. Act.	Pnx. '49 to '50; Pnp. '50 to '51; Sm. & PAS intermit.; INAH 1/53 to discharge
34	A.L.C.	2684	C	32	F	2/51	Influenzal	6/19/51	F.A. Act.	Sm. & PAS. 8/51 to 8/53 INAH 11/52 to 3/53

(Continued on next page)

TABLE I—*Continued*

ANALYSIS OF 34 CASES HAVING PULMONARY SURGERY

CODE:
I. & K.—infiltrates and cavity
tpy.—thoracoplasty
Sm. & C.—smear and culture
atel.—atelectasis
decort.—decortication
tub.—tubercle
Pn.—pneumonectomy
pnp.—pneumoperitoneum
arr.—arrested
fibr.—fibrosis
cas.—caseous
sthzd.—streptohydrazid
c.—with

No.	Initial	Case Number	X-ray	Adm. Sp	Surgery	Bact. of Specimen	Course	Pathology of Specimens
1	I.A.	3572	Infil. & K.	+	R.U. Lobe 9/53	— Sm. — C	Disch. 6 mos. arr.	Atel. fibr., K. only a slit, no cas. left
2	W.W.	3053	I & K	+	R.U. Lobe 8/53	— Sm. — C	Disch. 6 mos. arr.	Atel. K. only a slit, no cas. left
3	R.B.	1582	Infil.	+	L. Pnec. & tpy. 1/54	+ Sm. + C	Disch. 6 mos. arr.	Atel. upper, fibr., cas. masses lower
4	C.H.	2091	I & Ks	+	L. Pnec. & tpy. 10/53	+ Sm. + C	Disch. 6 mos. arr.	Atel. fibr., stellate scars; 3 cm. K., encap. masses
5	M.B.L.	2050	I & Ks	+	R.U. Lobe 12/52	— Sm. — C	Disch. 6 mos. arr.	Atel. lobe, scars, calc. tub., no Ks.
6	J.B.	3350	I & K	+	Ap. Post. Seg. L.U.	— Sm. — C	Disch. 6 mos. arr.	Atel. large stellate scar
7	H.L.	1551	I & K	—	Ap. Post Seg. L.U. Wedge Sup. Seg. L.L. 2/54	— Sm. + C	Disch. 6 mos. arr.	Healed tub., cas. masses, sm. K.
8	N.L.	3415	I & K	+	Ap. & Post Seg. R.U. 1/54	+ Sm. + C	Disch. 6 mos. arr.	Sm. K. in center segment, soft walled
9	M.P.	2599	I & K	+	R.U. Lobe and Wedge R.L. 1/54	+ Sm. + C	Disch. 6 mos. arr.	Ragged K. R. U. 2 by 1½ cm.
10	T.L.Y.	3107	I & K	+	L.U. Lobe 10/53	— Sm. — C	Disch. 8 mos. arr.	Healed K. stellate scar, calc. & fibr.
11	C.W.	3280	I & K	+	Ap. Post Seg. L.U. 1/54	+ Sm. + C	Disch. 6 mos. arr.	Sm. residual K., lcm. several cas. tub.
12	D.D.	3548	I & K	+	Ap. Post Seg. L.U. 1/54	— Sm. — C	A.M.A. 6 weeks, "lost."	Stellate scar of healed K., encap. tub.
13	D.V.W.	3447	I & K	+	L. Pn. 3/54	+ Sm. + C	Disch. 5 mos. arr.	Lg. 7 cm. K.; sm. 2 cm. cavities; cas. & calc. tub.
14	M.G.	3003	I & K	+	L.U. Lobe & Sup. Seg. L.L. 12/53	+ Sm. + C	Died 30 days, pul. embolism	Lg. 7 cm. K. in upper c thick wall; encapsulated tub.
15	C.G.	2383	I & K	+	Ap. Post & Ant. Seg. of L.U. c. decort. 12/53	+ Sm. + C	Ultimate disch. arr.	Large thick walled K., fibr., new K. closed 4-53 by tpy. ultimately arr.

16	W.R.	2950	I & Ks	+	R.U. Lobe c tpy.	— Sm. — C	Disch. 6 mos. arr.	Lg. thick walled K., smaller Ks., tubercles
17	W.C.B.	2605	I & K	+	R.U. Lobe 3/54	— Sm. + C	Disch. 6 mos. arr.	Sm. residual K., encap. tub.
18	F.H.	3615	I & Lg. K	+	R.U. Lobe 3/54	— Sm. — C	Disch. 5 mos. arr.	Large stellate scar under adhesion, encap. tub.
19	E.B.	2586	I	—	Ap. & Post Seg. R.U. 12/53 c decort.	+ Sm. — C	Disch. arr.	Several large cas. masses—one penetrating bronchus
20	W.J.	3192	I & K	+	R.U. Lobe 3/54	+ Sm. + C	Disch. 5 mos. arr.	Lg. flat, thick walled K. c lung stone; partly re-epith.
21	D.S.	3760	I	+	Ap. Post Seg. L.U. 4/54	+ Sm. + C	Disch. 6 mos. arr.	Lg. soft mass opening into bronch; several soft masses
22	E.S.	2107	I & Lg. Ks	+	Pn. & Tpy. 3/54	— Sm. — C	Disch. arr.	Lg. 10 cm. K. in upper c several small Ks—all smooth walls; fibr., some atel.
23	M.C.	3529	I	+	Ap. Post Seg. L.U. 4/54	+ Sm. — C	Disch. 5½ mos. arr.	Few encap. tub., no Ks.
24	R.F.	3286	I & Lg. Ks	+	R.U. & Mid. Lobe c decort. 9/53 Br. pl. fistula, emp. tpy. 4/54	+ Sm. + C	Died 3 days after tpy. Ps. aruginosa infection	Soft infiltration throughout; Lg. soft walled K. in upper; pleuritis; empyema
25	G.R.	3304	I & K	+	R.U. Lobe c decort. 3/54	— Sm. — C	Disch. arr.	A fibr. mass c residual K. 1 x 1½ cm. thick pl.
26	W.B.	3530	I	+	Wedge R.U. 3/54	— Sm. + C	Disch. 4 mos. arr.	Sm. residual K 1 x 1½ cm.
27	L.F.	1534	I & Ks	+	L. Pn. & tpy 5/54	+ Sm. + C	Disch. 5 mos. arr.	Many Ks, fibr., atel., tub.
28	L.W.	3135	I & K	+	R.U. Lobe 2/54	+ Sm. — C	Discharged arr.	Residual K 1½ cm., encap. tub.
29	S.C.	3239	I & K	+	L.U. Lobe 4/54, then R.U. Lobe 5/54	— Sm. + C	Disch. 3 mos. arr.	Large stellate scar, encap, tub. bronchiectasis
30	K.J.	379	I & Ks	+	L.U. Lobe 1/54	— Sm. — C	Pneumothorax, but disch. 8 mos. as arr.	Inspissated K. and 2 scars of healed Ks
31	H.M.	3567	I & K	+	Post tpy. L.U. Lobe 5/54	— Sm. — C	Disch. arr.	Atel; small residual K., re-epith.
32	L.O.	2689	I & K	+	R.U. Lobe 7/53 followed by tpy. for Broncho. pl. fistulae 8/53	— Sm. — C	Downward course Died 9/10/53	Large ragged K. c pyogenic wall; many cas. tub.
33	E.W.	3373	I & K	+	R. Pn. c tpy. 2/5/53	— Sm. — C	Disch. 10 mos. arr.	Several residual Ks.; fibr.; atel; endobronchitis; stellate scars
34	A.L.C.	2684	I & K	+	R.U. Lobe 3/6/53	— Sm. — C	Disch. arr.	Large stellate scar with many encap. tub.

There is perhaps nothing that has not happened before, and actually been described before, but the difference is in the number of occurrences and the reduced time in which they occur. In fact, one of the authors (H. C. S.) and others have described practically every change to be described subsequently in this paper. The difference is that, following the best antimicrobial therapy with proper collateral treatment, there is a gradual healing of tuberculous lesions up to the point of emergence of resistance, or to the break of the patient's strict regimen in one way or another when a reversal of the healing tendency may result. It may be stated rather dogmatically that the majority of untreated cases of tuberculosis may be brought to healing by vigorous and proper treatment. The principal failures are due to improper treatment, or to disease that is too far advanced or too chronic at the beginning. Even far advanced lesions may be brought to a point of freedom from tubercle bacilli. Large caseous foci or fibrotic and encapsulated lesions, however, may shield bacilli for long intervals so that only partial healing will result with prolongation of activity, continuance of the presence of acid fast bacilli and even exacerbation and extension of the disease as a result of the emergence of resistant bacilli.

The material in this study is a representation of various types of healing, some of which would have recovered without resection, but most of the cases were brought to an arrest by the intervention of surgery following, and along with, antimicrobial therapy.

It should be mentioned that there were a rather large number of resections carried out before bacteriological control methods were established, but it was thought better to work with a smaller series where more complete work was done, than with a larger series with incomplete studies.* Unfortunately it was not possible to complete the virulence studies on the 15 positive cultures in this series.

There are 34 cases in the groups which are listed in Table I. Many details are included, some of which are worthy of discussion. Others are statistical or only of academic interest.

There were 18 females—12 white and six colored; 16 males—nine white and seven colored. The average age of the females was 28.8 years—27.3 for the white and 32 for the colored. The average age of the males was 38.6 years—39.2 for the white and 38.0 for the colored.

There was evidence of cavity on x-ray film in 29 cases—some had huge and multiple cavities.

All cases but two had positive sputum on admission. They had been positive at an early date. The onset of symptoms were uneventful and about as expected from many former reports. Drug treatment was generally adequate and satisfactory, but several cases had been treated most irregularly.

The course of the disease was favorable, ending in arrest in about six months in all but three cases.

*At this juncture we should like to pay tribute to our colleague Dr. Leffie Carlton, who did most of the early resections and several in this series.

As to the type of the surgery performed, six (3, 4, 13, 22, 27, 33) had pneumonectomy, only one (13) without concomitant thoracoplasty. Two were on the right (22, 33) and four were on the left (3, 4, 13, 27). All survived and were discharged as arrested within six to 10 months. Eight (1, 2, 5, 17, 18, 20, 28, 34) had simple right upper lobectomies and all were discharged within five to eight months as arrested. Two (16, 32) had right upper lobectomies with thoracoplasties, one died following bronchopleural fistula and thoracoplasty, the other was discharged, arrested within six months. One (25) had right upper lobectomy with decortication that was discharged as arrested. Another, (24) had right upper lobectomy with decortication followed by broncho-pleural fistula and thoracoplasty but succumbed to a *Ps. aruginosa* infection. Another, (9) had right upper lobectomy with a wedge of the right lower and was discharged in 6 months. There was one (26) having a wedge resection of the left upper that was discharged within four months as arrested. There were only three (10, 30, 31) left lobectomies of which one, (31) was post-thoracoplasty. All of these were discharged before 10 months as arrested—one after hemathorax with recovery. There was one (14) left upper lobectomy with a superior segment of the left lower that died within 30 days of a pulmonary embolus. The patient was making an uneventful recovery. One (29) had had left upper lobectomy, followed within 30 days with right upper lebectomy. This patient was discharged within three months after the second operation as arrested.

Two (8, 19) had apical posterior segmental resections, the latter (19) with decortication. Both were discharged as arrested.

Five (6, 11, 12, 21, 23) had left apical posterior segment removed, five were discharged within six months as arrested, one was A.M.A. within six weeks, but was in good condition when he left.

There was one (7) having an apical posterior segment of the left upper, with a wedge of the superior segmant of the left lower, that was discharged in six months as arrested. One (15) had apical posterior and anterior segment of the left upper with decortication and ultimately discharged as arrested.

Seventeen of the operations were on the left side and 16 on the right side. One was bilateral. The tendency seemed to run toward right upper lobectomies, with segmental operation on the left. There was usually more good lung tissue left on the left side than on the right. Otherwise, the two sides had no essential difference.

Bacteriological results are tabulated in greater detail in Table II.

There were 15 specimens negative on smear and culture; 12 positive on smear and culture; four negative on smear and positive on culture, and

TABLE II
BACTERIOLOGICAL FINDINGS IN RESECTED SPECIMENS

Negative Smear and Culture	Positive Smear and Culture	Negative Smear Positive Culture	Positive Smear Negative Culture
15	12	4	3

three positive on smear and negative on culture. Virulence tests were not completed. Results of the three cases negative on culture, but positive on smear were similar to the findings of others and were not greatly unlike the findings in patients not treated with antimicrobials. There is no doubt a more sudden and detrimental effect on the bacilli produced by the drugs, but it probably represents, in part at least, only an accelerated process of the same phenomenon. Many times bacteria may be shut off from oxygen and nourishment so that they may be thought of as existing in a gradually progressive dormant state until death finally ensues. It is possible that many of the bacilli may be revived from this state with proper enrichment of culture media and improvement of environment, but undoubtedly a time will come, perhaps rather suddenly in bacilli exposed to antimicrobials, when it is impossible to elicit growth and reproduction by any known method.

The problem is largely an academic one, since most of the bacilli

TABLE III

ANALYSIS OF 34 RESECTED LESIONS WITH REGARD TO BACTERIOLOGIC AND PATHOLOGIC CHANGES

Pathologic State of the Resected Lesions	Number	Percentage	Bacteriologic Findings	Surgical Needs	Case Number
No cavities on X-ray and none found after surgery—essentially healed	2	5.9	1 + Sm + C 1 + Sm − C	Questionable need, except to remove useless and dead tissue, but justifiable	3, 23
Cavities and tubercles closed by fibrous tissue completely or with only residual slits	9	26.4	8 − Sm − C 1 − Sm + C	No apparent need except to remove dead tissue	1, 2, 5, 6, 10, 12, 18, 29, 34
Cavities closed to apparently 1 cm. in diameter	5	14.7	All + C 2 + Sm	Justifiable but—may have recovered without surgery	7, 8, 11, 17, 26
"Cystic Lung" residue—otherwise healed	1	3.0	1 − Sm − C	Necessary to remove future threats of a non-specific nature	22
Large caseous masses—two with no cavities on X-ray, but did not show beginning cavities pathologically. One was old cavity with inspissated pus	3	8.8	1 + Sm − C 1 − Sm + C 1 − Sm − C	Absolutely necessary	19, 21, 30
Various combinations of large cavities—thick walled or containing inspissated pus—with or without atelectasis, encapsulated caseous or calcified tubercles—recovered	11	32.4	6 + Sm + C 1 + Sm − C 4 − Sm − C	Imperative for Survival	4, 9, 13, 15, 16, 20, 25, 27, 28, 31, 33
Same as preceding, but fatal within 60 days or less	3	8.8	2 + Sm + C 1 − Sm − C	Imperative	14, 24, 32
	34	100.0			

probably go on in time to death. Although there may be certain signs of life in the protoplasm for periods of time long after growth reactions have ceased. It may be compared to higher forms of life. The cells of a tree do not die immediately after it is cut down and the cells of an animal live long after the heart stops beating.

The analysis of the 34 resected lesions with regard to the nature of the pathology and the prognosis at the time of operation is presented in Table III.

There were nine (1, 2, 5, 6, 10, 12, 18, 29, 34,) having complete closure of cavities with encapsulation and resorption of all foci. These cases showed at the most only thin slits or small inconsequential cavities in a few millimeters in diameter. Some of the cavities were completely filled in with granulation tissue. In retrospect, it is apparent that most of these cases probably would have recovered without surgery, since only one had a positive culture on the resected specimen.

Two (3, 32) that showed no cavities on x-ray films, cleared almost entirely, but one specimen was positive on smear and culture and the other on smear. The need for surgery was doubtful, but justifiable in view of the bacillary findings. It is likely that both cases would have recovered in time without operation.

The third group was represented by five (7, 8, 11, 17, 26) where there were definite cavities remaining but they were shrunken to less than 1½ cm. in diameter. All specimens were positive on culture and two were positive on smear. In view of the positive cultures, surgery was entirely justifiable, although most of these cases may have recovered in time, especially if proper rest and antimicrobial therapy were applied.

One case represents a group that needs special consideration. It is the acute pneumonic type that responds well to drug therapy—so well that there is a disappearance of sputum and tubercle bacilli. This case (22) was negative for a year previous to operation. The cavities did not disappear, but remained open, perhaps by valvular mechanism. Some appeared to have become "tension" types—assuming the appearance of a cystic process. The walls of these cavities tend to become thin plates of connective tissue with no epithelium. In fact the surface is smooth and free of all caseation and granulation tissue. As the illustration shown by the case of B. L. No. 3414, these "bullae" may form, enlarge and disappear and the whole process may gradually shrink upwards towards the apices.

The next group of three (19, 21, 30) represents the group containing large, caseous masses, caseous "unresolved" infiltrates, or shrunken cavities containing inspissated pus and "tuberculomas" of several types. These cases rarely recover spontaneously, but remain a threat for years and even decades. Surgery is not only justifiable, but mandatory in spite of the fact that the case (30) with inspissated pus in the old cavity revealed no tubercle bacilli in the specimen.

The most important group of all includes many types of pathology with large, and sometimes many thick walled cavities, some containing

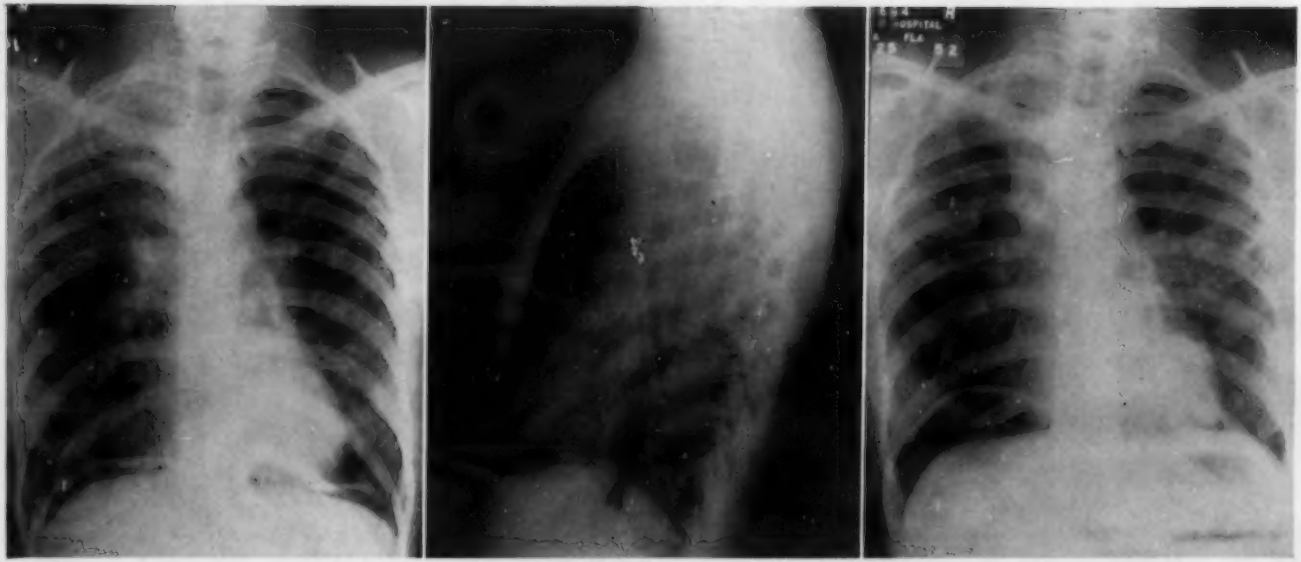


FIGURE 1 FIGURE 2 FIGURE 3

Figure 1: An A. P. roentgenogram of Case 34, taken April 23, 1951, showing an 8 cm. annular shadow in the right apex. There is a residual pneumoperitoneum.—*Figure 2:* Same case, taken July 25, 1951, with a lateral roentgenogram showing the same annular shadow.—*Figure 3:* Same case on January 25, 1952, with greatly reduced annular shadow in the apex and an extension of an infiltrative process into the left midfield. This exacerbation followed a disciplinary discharge.

inspissated pus, some with areas of atelectasis, some with diffuse fibrosis, some with many encapsulated masses, other with caseous and calcified tubercles and many other combinations. Most of these cases have destroyed lungs that must be removed by pneumonectomy. Others need lobectomy alone, or with added segmental or wedge resection. Others may only need single or multiple segmental resection, but all have a grave prognosis and their salvation depends almost entirely on surgery.

The greatest problem in tuberculosis hospitals today is to treat these far advanced, mostly bilateral cases until they become amenable to surgery and the greatest challenge of the chest surgeon is to devise ways and means of operating on these "salvage," or at least serious types of case. Of this group of 11 (32.4 per cent of the series) (4, 9, 13, 15, 16, 20, 25, 27, 28, 31, 33) six were positive on smear and culture. One was positive on smear alone, and in four no tubercle bacilli could be found. In spite of the favorable bacteriologic finding in the last four, the surgery was mandatory since there were large numbers of unhealed tubercles, cavities, and other pathology that would have been a long time in healing if it ever would heal.

The last group of three (14, 24, 32) are those that died. One (24) succumbed to a *Ps. aruginosa* infection that was apparently present at the time of operation and which did not yield to the measures adopted. A broncho-pleural fistula developed for which thoracoplasty was done. There was not realization of the seriousness of this infection either before operation or during the first days after. In fact, the patient was practically lost before the bacterial diagnosis was made. Another case (14) died 30 days after operation as a result of a pulmonary embolus. This

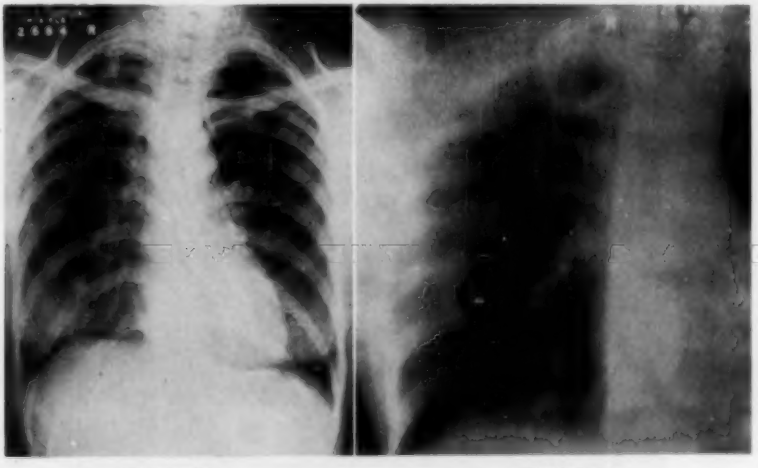
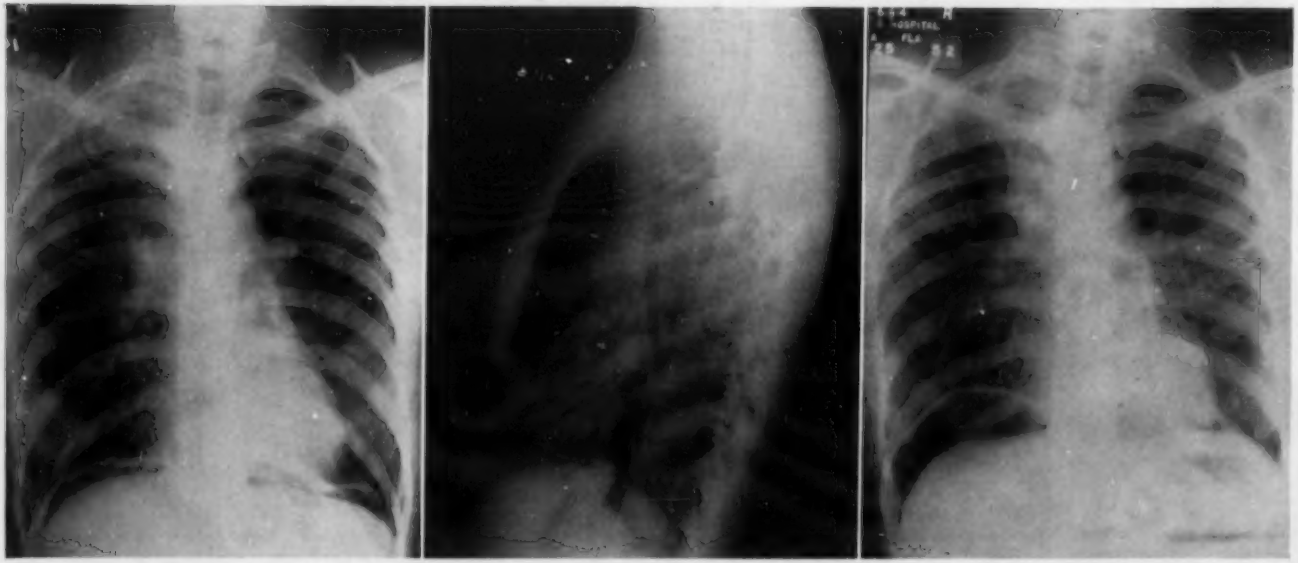


FIGURE 4 FIGURE 5

Figure 4: Same case on December 15, 1952, after readmission with a sharp outline of a smaller cavity in apex and a clearing of midfield.—*Figure 5:* Same case on February 17, 1953, with an A. P. planigram, showing a sharply outlined annular shadow.



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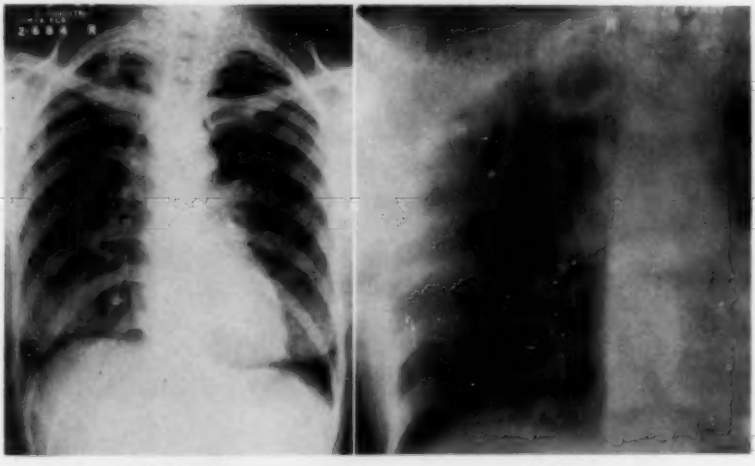

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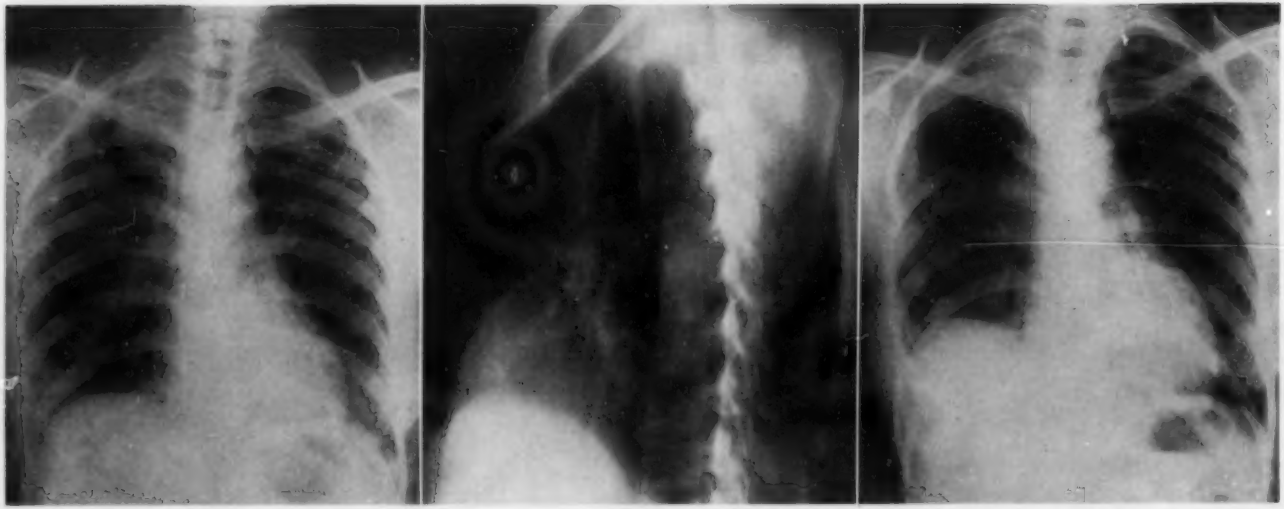

FIGURE 6 FIGURE 7 FIGURE 8

Figure 6: Same case on March 23, 1953, with no definite annular shadow remaining.—*Figure 7:* A planigram at later time with nothing but an irregular shadow.—*Figure 8:* Same case on June 18, 1953 after surgery.

patient was a fine risk before and after operation, but the patient followed a rest program so well that the thrombi developed in the femoral veins unbeknown to anyone. The other case (32) was a poor risk before operation, developed a bronchopleural fistula, followed by thoracoplasty, but succumbed within 60 days of the first operation. It belonged to the group of cases that must remain as the "calculated risk" in tuberculosis.

In order to illustrate in greater detail some of the chief pathological changes, seven cases will be given in more detail, one of which was not operated on, but it is intended to represent a special type of cystic lung similar to one of the operated cases.

The six operated cases illustrated different types of involvement from complete healing of large cavities to a heterogeneous mixture of healing, partial healing, arrest of healing and many other types of pathology.

The various cases will progress in the reverse order of healing rather than in sequence in numbers. For example, those showing the most striking healing will be given first.

Case 34: A. L. C., 32 year old colored female, was admitted to the Southwest Florida Tuberculosis Hospital on June 19, 1951, with a diagnosis of far advanced, active pulmonary tuberculosis. Onset of tuberculosis was apparently in February, 1951, at which time the patient was diagnosed as having influenza. She failed to respond to the usual symptomatic treatment and x-ray films subsequently disclosed tuberculosis.

Antibiotic therapy consisted of isoniazid (INAH) daily from November 14, 1952;

FIGURE 9: Gross specimen of Case 34. Note the large depression in the upper aspect with attachment of adhesion. The depression in the mid-zone is artefact.

FIG. 10

FIG. 11

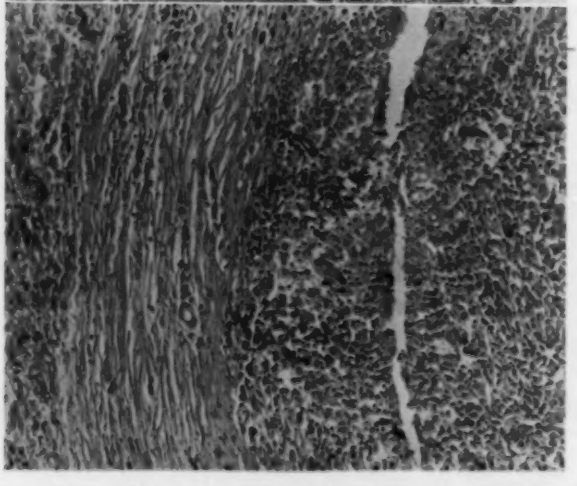

Figure 10: Low power microphoto of a section through the depression shown in Fig. 9. Note stellate scar with only a few slits remaining. The whole scar was several centimeters in length. The roof of the cavity seemed to have fallen in. X6 H & E—
Figure 11: A higher power magnification of the area outlined in the rectangle. Note the remaining slits with fibroblasts on each side and heavier bands of connective tissue. X30. H & E.

para-aminosalicylic acid (PAS) daily since August 13, 1951, and streptomycin twice weekly since August 13, 1951. All three drugs were continued through the period of surgery and for several months subsequent to surgery.

Right upper lobectomy was performed on March 26, 1953, for residual tuberculous atelectasis and "cavitation."

Pathologic Findings: The specimen consisted of a right upper lobe. There was an adhesion on the upper aspect of the lobe with a deep depression beneath it. On section there were many strands of fibrous tissue on the cut surface. The principal fibrous remnant was beneath the depression in the pleura.

The microscopic specimen revealed the depression in the pleura and the heavy band of fibrous tissue running irregularly throughout the specimen. The main band of tissue ran parallel to the surface of the pleura. There were many branches running out from the main band, like skeins of yarn. A higher magnification reveals a thin slit with fibroblasts forming on each side to bridge the gap. All caseous material has been resorbed along with all polymorphs and other constituents of a pyogenic membrane.

Case 18: F. H., 29 year old colored female, was admitted to Southwest Florida Tuberculosis Hospital on October 13, 1953, with a diagnosis of moderately advanced, active pulmonary tuberculosis. Sputum on admission was positive. Onset of disease occurred in May, 1952, at which time she noticed loss of weight, malaise, cough and expectoration. She was hospitalized from June, 1952 to January, 1953, in another institution and received 250 mgs. daily of INAH at that time. She showed considerable improvement but was discharged in a disciplinary status and apparently did not remain under treatment until admission to this institution.

Antibiotic therapy given prior to surgery consisted of INAH, PAS, from October 25, 1953, until March 18, 1954. Bacteriological studies of the resected specimens were negative on smear and culture for acid-fast organisms. Convalescence was uneventful and she was subsequently discharged as an arrested case.

Pathologic Findings: The specimen was the upper lobe of the right lung. A few fresh tubercles were noted and in the upper part of the lobe, there

FIGURE 12

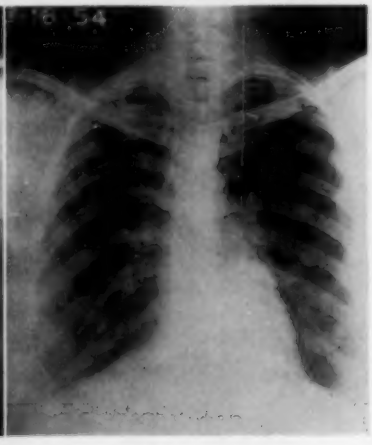

FIGURE 13

Figure 12: A print of an A. P. roentgenogram of Case 18, taken on June 30, 1952, showing involvement of the whole right upper lobe with a 10 by 12 cm. cavity.—*Figure 13:* Same as Fig. 12, taken on March 16, 1954, just before surgery. There is little left of the infiltration and the cavity is not visible.

was a stellate scar measuring about 1½ to 2 cm. across with projections running out into the tissues, indicating the site of previous cavitation. The cavity had apparently become entirely filled in with granulation tissue.

FIG. 14

FIG. 15

Figure 14: A low power microphoto of a section through a spider-shaped scar in the upper part of the resected lung lobe. The scar was about 0.5 by 1.5 by 2.5 cm. in dimensions. X6 H & E.—*Figure 15:* A higher magnification of the outlined area in Fig. 14. Note the caseous central area and the ring of lymphocytes around all that is left of the cavity. Bands of fibrocytes are outside the lymphocytes. X30 H & E.

In other areas of the specimen, complete healing was noted. There was a small homogeneous mass in the center with a ring of cells arranged in elliptical manner.

The microscopic section revealed a tangled mass of organized connective tissue with a small central caseous focus surrounded by lymphocytes. There had apparently been complete obliteration of the pyogenic membrane on the surface of the cavity, with a replacement of the neutrophiles by lymphocytes and a gradual closing of the opening until nothing was left but a small area of caseation that was being resorbed by a centripetal encroachment of lymphocytes.

Case 6: J. B., 55 year old white male, was admitted to the Southwest Florida Tuberculosis Hospital on December 20, 1952, with a diagnosis of far advanced, active pulmonary tuberculosis. Sputum was positive for acid-fast bacilli on admission. Onset of illness began two years prior to admission with progressive weakness, loss of weight, and cough. Chest roentgenograms revealed cavitation in the left upper lobe and an infiltrative process in the right apex.

Antibiotic therapy consisted of streptohydrazide from January 8, 1953 until November 27, 1953; streptomycin from November 27, 1953 to December 4, 1953. This was continued subsequently to surgery as has been routine in all cases. Sputum converted to negative in March, 1953.

Resection of the apical-posterior segment of the left upper lobe was performed on December 4, 1953, for residual infiltrative and fibrotic disease. Bacteriological studies of the resected specimen were negative on smear and culture for acid-fast bacilli. Subsequent course was uneventful and the sputum remained negative until he was discharged.

Pathologic Findings: The specimen consisted of an apico-posterior segment of the left upper lobe containing a large central stellate scar. This unquestionably represented the site of the previously noted large apical cavity that had undergone complete healing. The area of the scar was filled with solid granulation tissue. A small secondary cavity

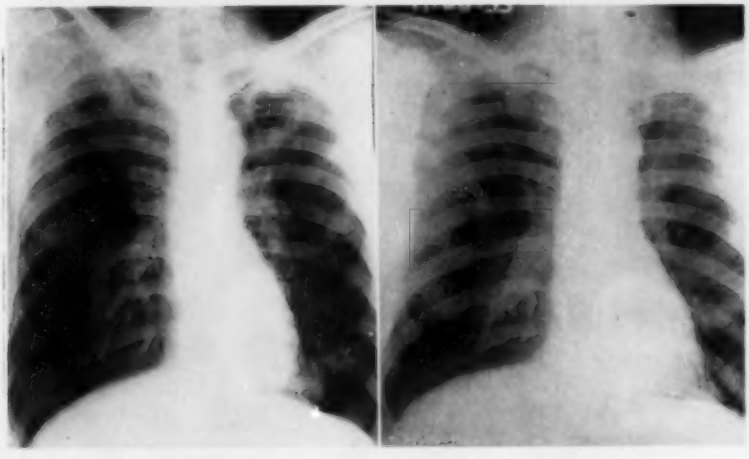

FIGURE 16 FIGURE 17

Figure 16: An A. P. roentgenogram of Case 6, taken on December 23, 1952. Note the large cavity in the left upper and infiltration in the right apex.—*Figure 17:* Same case as Fig. 16, taken on November 30, 1953. Note the clearing of infiltrations with no sign of a cavity wall shown in Fig. 16.

FIG. 18

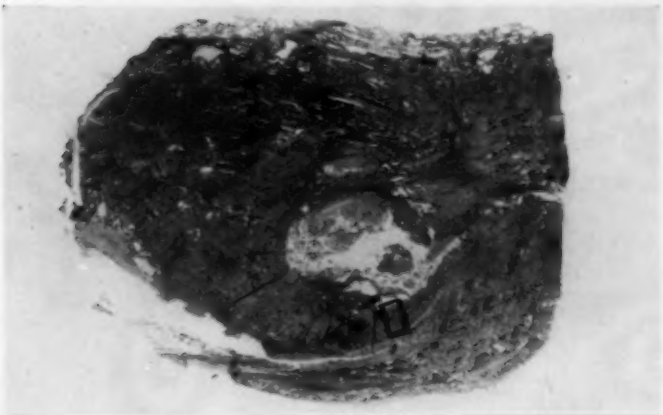

FIG. 19

Figure 18: A low power microphoto of the fibrous scar in the upper part of the specimen. There is only a 3 mm. cavity left. X6 H & E.—*Figure 19:* A higher magnification of area outlined in rectangle in Fig. 18. Note the clearing caseation with atrophic granulation tissue. X30 H & E.

with a ragged center was noted in the extreme apex and this measured approximately 1½ cm. in diameter. There were no tubercles found in the lymph nodes, or tuberculous ulcers in the bronchial tree.

The low power microscopic view consisted of a field of solid fibrous tissue with a 2-3 mm. opening in the center. A higher magnification of the wall of this opening revealed atrophic granulation tissue. There were "ghosts" of capillaries and fibroblasts remaining with no caseation, nor other cellular remnants. The small cavity in the apex was typical of a static process with disintegrating cellular debris, undergoing caseation. The large cavity had all but closed, but the small sub-pleural cavity had not entirely closed.

Case 3414: (Figs. 20 to 23 incl.) A 19 year old colored female was admitted to the Southwest Florida Tuberculosis Hospital on January 18, 1953. Admission diagnosis was far advanced active pulmonary tuberculosis. She was extremely ill at the time

FIGURE 20 FIGURE 21

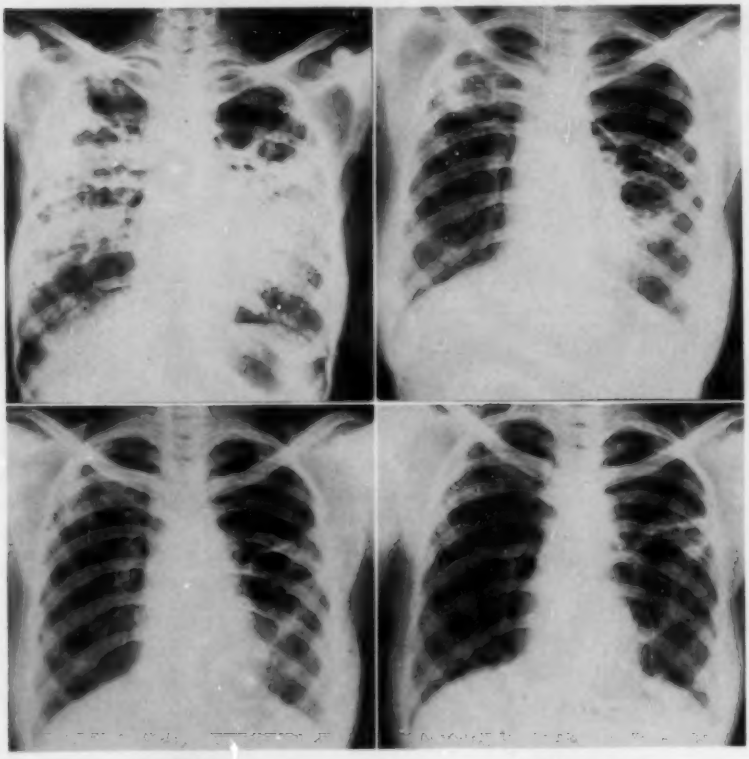

FIGURE 22 FIGURE 23

Figures 20, 21, 22, 23: A. P. roentgenograms of patient B. L., Case 3414, showing a remarkable clearing of the pneumonic caseation and infiltration shown in Fig. 20. The dates of the x-rays are February 19, 1953; November 25, 1953; February 5, 1954; and May 13, 1954. It will be observed that bullae form and enlarge, due perhaps to a valvular mechanism of the draining bronchi. The patient has been bacillus negative for over 18 months. The net result is a cystic lung. This case is similar to Case 22.

of admission and the prognosis was considered poor. Her sputum was positive for tubercle bacilli.

Her history was one of progressive cough, expectoration, fever, weight loss and night sweats for the previous six month period. Chest roentgenogram on admission showed

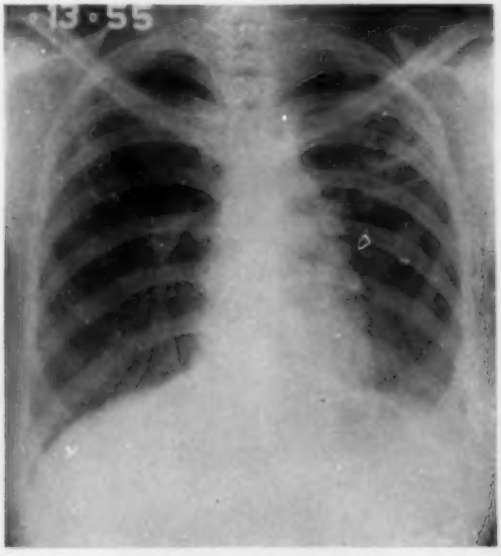

FIGURE 24: Same as Figs. 20-23 on January 13, 1955. Note the shrinking of the cavities in the left upper. This process has no doubt been augmented by the Monaldi drainage.

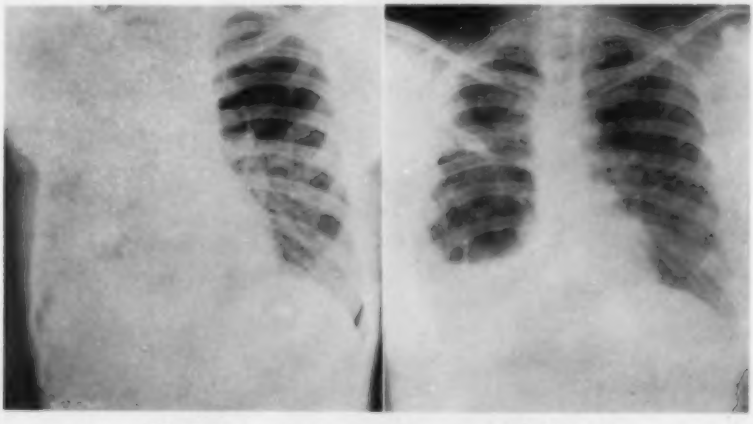

FIGURE 25 FIGURE 26

Figure 25: An A. P. roentgenogram of Case 22, taken on February 10, 1950, showing a pneumonic consolidation of the whole right lung with much infiltration in the left base.—*Figure 26:* Same as Fig. 25, taken on March 2, 1954, showing clearing of most of the infiltrations with huge residual cavities in the upper and lower lobes. The cavities were essentially bullae with smooth and shining walls and no caseation or granulation tissue. The lung after removal was a collection of many dark, reddish brown, flaccid bullae, with walls of one to several mm. in thickness.

diffuse tuberculous pneumonic consolidation and infiltration throughout both lung fields. There was a definite family history of tuberculosis, one of the brothers having recently died of tuberculosis in a tuberculosis hospital. Her father had also succumbed to tuberculosis several years ago. She was immediately placed on streptomycin, PAS and INAH, due to the critical nature of her illness.

Following one month of therapy there was excellent radiographic improvement. The therapy conference at the end of six months noted that her improvement had been dramatic, although the case still presented many problems.

On September 7, 1954, Monaldi drainage was performed for the purpose of decreasing the size of a large left upper lobe cavity. This attempt was not entirely successful and she appeared to tolerate the drainage tube poorly. As of the present time, she continues to show progressive improvement although there is still large visible bilateral apical bullae. In time, one side may clear enough to permit surgery on the other. Rarely these large bullae may close spontaneously. Sweany, Perez and Dietrich[16] reported a case where the whole left upper lobe was excavated, but closed so that an opening of no more than a cm. remained. At present there are probably 25 per cent of advanced cases that are not amenable to surgery, but by patient and correct drug treatment, many will in time become operable and even arrested. One of the greatest challenges of the tuberculosis physician today is to bring as many of these cases to surgery as possible. On the part of the surgeon, it is his challenge to devise ways and means to operate on such cases successfully.

The medical therapy was as follows:

Streptomycin	0.75 Gm. biweekly	2-21-53 to 11-30-53	Discon'd due to weakness
INAH	1000 mg. daily	2-21-53 to 2-25-54	
	500 mg. daily	2-25-54 to 12-24-54	
	500 mg. daily	12-27-54 to 1- 1-55	
	200 mg. daily	1- 2-55 to 1- 8-55	
	200 mg. daily	1- 9-55 to ——	
PAS	12 Gm. daily	2-21-53 to 1- 9-55	

(INAH and PAS are still being administered and lung not yet resected.)

Case 22: E. S., a 30 year old colored female, was admitted to the Southwest Florida Tuberculosis Hospital on February 9, 1950, with a diagnosis of far advanced, active pulmonary tuberculosis. Sputum was positive on admission. Onset occurred in December, 1948, with a severe pleuritic type of pain in the right chest. There was also cough, fever and night sweats. X-ray films revealed extensive bilateral disease which was diagnosed as tuberculous pneumonia.

In addition to modified bed rest, hospital treatment consisted of streptomycin and PAS beginning March 7, 1950 and given intermittently during the subsequent four years. INAH was started on August 6, 1952. Following the institution of the INAH therapy, a remarkable clinical and radiological improvement was noted. The previously consolidated destroyed right lung became a mass of large blebs and bullae. This lung was considered to be a functionless, destroyed, multicavitary organ and represented the characteristic method of healing frequently seen following administration of INAH. Right pneumonectomy and concomitant thoracoplasty was performed on April 20, 1954. Bacteriological studies of the resected specimen were negative on smear and culture for acid-fast organisms. Post-operative course was uneventful and she was subsequently discharged as an arrested case.

Pathologic Findings: The specimen represented a destroyed right lung. The lung was completely consolidated and carnified and there was evidence in the bronchi of old healed bronchitis. Scars of former ulceration could still be seen. There was extensive bronchiectasis involving the lower lobe and the entire apical area was replaced by a large cavity measuring 10 centimeters in diameter. This apparently had been completely sterilized. The wall of this cavity composed of a slick surface resembling that of any mucous membrane. There was no caseation remaining, nor any signs of inflammatory reaction.

Microscopic: The wall of the large cavity was a compact layer of fibrous connective tissue with what appeared like a remnant of a venous sinus in the center. The exposed surfaces had no evidence of epithelium whatever. It was bare connective tissue that had developed a smooth surface.

This phenomenon has been described by Bernard and associates[17] in four cases with "recent, acute and exudative type lesions," following antibiotic treatment.

Pruvost and associates,[19] Simonin and associates,[20] Bernou,[21] Jacob and associates[22] and others have also recorded the phenomenon.

Galy[18] and associates described three resected specimens which were interesting pathologically. The walls of the "bullae" were composed of smooth connective tissue with no secretions or epithelial covering.

The formation of "bullous cavities" seems to be due to several factors. First, there is a recent acute infection where nothing but rapidly growing bacilli are present. These bacilli are attacked by the antibiotic, especially INA, and seem to be wiped out in toto before resistant forms can appear. It is the same result Steenken obtained in rabbits where he felt that he had sterilized the lesions and that all bacilli were dead. Furthermore, there were no "dormant" bacilli or "granules" left to light up an infection later, or to develop into resistant forms.

After the sterilization of the lesions the cavities remain open because the bronchi entering the cavities protrude into the lumen as valve-like mechanisms. This causes a gradually increasing tension within the cavity. As a result the cavities become much enlarged. In the case reported there was a case of adhesive pleuritis that kept the whole lung from

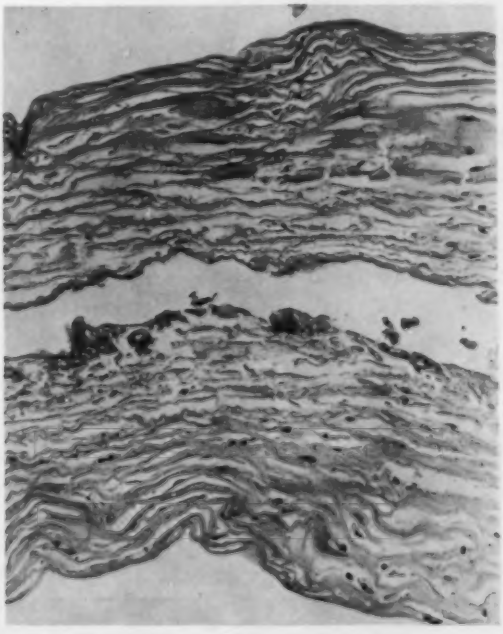

FIGURE 27: A microscopic photograph of a section through the walls of two adjacent bullae. There are two surfaces of bare connective tissue. There is no sign of epithelium. X190.

collapsing. There must be free pleural surfaces before such lesions can close out. When there is such a chance the lesions shrink and actually become closed, as reported by Sweany, Perez and Dietrich.[16] On the other hand, they may remain or actually enlarge as bullae.

Case 28: L. W., 28 year old colored male, was admitted to the Southwest Florida Tuberculosis Hospital on June 21, 1952, with a diagnosis of far advanced, active pulmonary tuberculosis. Sputum on admission was positive. Onset of illness apparently occurred in the early part of 1951 at which time the patient was in another tuberculosis hospital for several months.

In December, 1952, pneumoperitoneum was instituted and maintained until the time of surgery. Streptomycin and PAS were started in June 1952 and continued until

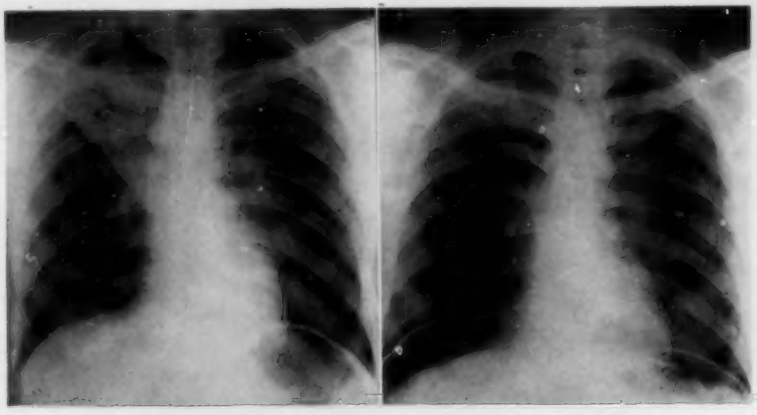

FIGURE 28 FIGURE 29

Figure 28: An A. P. roentgenogram of Case 28, taken on July 15, 1952, several years after the disease was first found and after several courses of antimicrobials. There is much contraction towards the apex.—*Figure 29:* Same as Fig. 28, taken on February 9, 1954. There has been much clearing of the infiltrations and a shrinking of the cavities to oblong slits.

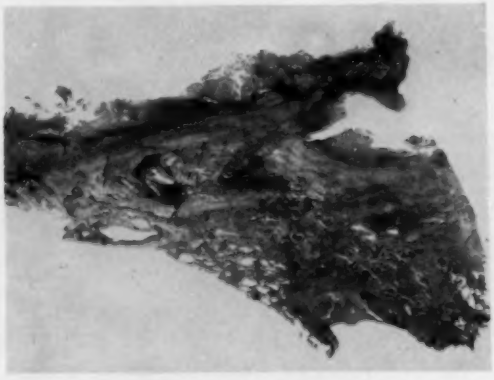

FIGURE 30: A low power of a section of Case 28 taken through the walls of some of the cavities. The smear of the caseation was positive, but the culture was negative. This patient had almost 4 years of intermittent antimicrobial therapy before surgery, part of time under commitment. X6 H & E.

February 12, 1954. INAH was added from September, 1952, until the present period. Although there was remarkable improvement in the inflammatory disease noted in the right lung, planigrams still revealed evidence of residual right upper lobe disease. On February 12, 1954, right upper lobectomy was performed. Bacteriological studies of the resected specimen were positive on smear and negative on culture for acid-fast organisms. Subsequent course was uneventful and he was discharged as an arrested case.

Pathologic Findings: The specimen consisted of a right upper lobe which contained almost complete healing of the tuberculous process. What was once a cavity measuring about 8 cm. in diameter had contracted down to a puckered area measuring 1½ to 2 cm. and filled with granulation tissue. A few small cyst-like areas were seen surrounding this zone and might still have represented part of the original cavitary process. The bronchi were slightly dilated throughout. The lobe itself consisted of atelectatic tissue with a slight amount of fibrous reaction around the bronchi. No active lesion could be found despite the fact that smears were positive.

Microscopic: The section shown is only one-half the whole specimen because of the size of the piece of tissue. The microscopic view revealed a heavy fibrous wall around a long thin slit of caseous material surrounded by a disappearing layer of granulation tissue.

The original cavity was reduced to a slit about 5 mm. at its greatest dimensions with several other caseous pockets in the specimen.

Case 33: E. W., 23 year old white female, was admitted to the Southwest Florida Tuberculosis Hospital on January 13, 1953, with a diagnosis of far advanced, active pulmonary tuberculosis. She had previously been a patient at the Tallahassee Tuberculosis Hospital in November, 1949 and was transferred here for surgery. Her original complaints had been chronic fatigue, productive cough, high sweats and hemoptysis.

Collapse therapy between 1949 and 1953 consisted of one year of artificial pneumothorax, left, and six months of pneumoperitoneum. Streptomycin and PAS had been administered intermittently during the four year period and was continued throughout her course of surgery. INAH was started upon admission to this institution and con-

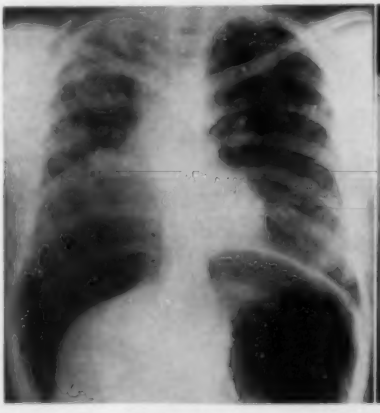

FIGURE 31

FIGURE 32

Figure 31: An A. P. roentgenogram of Case 33, taken on January 14, 1953, showing a diffuse involvement of the whole right lung with some clear spaces that appear to be cavities. There are also discrete shadows in the left midfield.—*Figure 32:* Same as Fig. 31, taken on February 3, 1953, with an increase in the densities on the right and an enlargement of the annular shadows.

tinued until the time of discharge, approximately 10 months later. X-ray findings prior to surgery showed a completely destroyed and atelectatic right lung with some nodular apparently healed disease throughout the left mid-lung field.

Right pneumonectomy and concomitant thoracoplasty were performed on February 5, 1953 uneventfully. Her subsequent course was satisfactory and she was discharged as an arrested case 10 months following pneumonectomy.

Pathologic Findings: The specimen consisted of an entire lung which was atelectatic, fibrotic and non-functioning. There were scattered nodules in varying sizes and varying ages of lesions throughout the lung. Some contained caseous material while others represented apparently healed scars. Several areas of open cavitation remained. Definite endobronchial disease was noted.

FIG. 33

FIG. 34

Figure 33: A low power microphoto from Case 33. (Figs. 31 & 32). There are many encapsulated tubercles, some clearing of the infiltrative areas and an increase in fibrous tissue throughout. X6 H & E.—*Figure 34:* A small cavity from another part of the lung. Some parts of the cavity wall are caseous with a partial clearing of the pyogenic wall. X6 H & E.

Microscopic: The microscopic appearance varied in different parts of the lung. The tubercles were heavily encapsulated with giant cells in the walls; there were strands and skeins of heavy fibrous tissue, and areas of resorption showing a more reversible type of infiltration. In one section there was an oblong cavity measuring 0.5 by 2 cm. In one end of the cavity was a remnant of a pyogenic wall with resorption of most of the cellular material. Part of the caseation still remained as a solid mass. In the other end of the opening was a remnant of granulation tissue. The caseation had apparently been replaced by granulation tissue and this in turn was disintegrating.

Discussion

There is little in the bacteriologic findings that needs comment. In fact, there were only three cases that were positive on smear, but negative on culture. This result could be accounted for in many ways: to technical variations, to chance, to inadequate culture methods, etc. The fact that 15 specimens were negative for all tests for bacilli, is only what could be expected in healing tuberculosis. I believe under the existing circumstance we are justified in saying that most of the tubercle bacilli in the samples taken were dead. While some of the bacilli grew, we do not know how many of the acid fasts showing on smear, were past the point where recovery of growth were possible. In fact, it seemed in some cases, there were many more bacilli on smear than appeared as colonies on culture.

What might have been found if every part of the specimens were

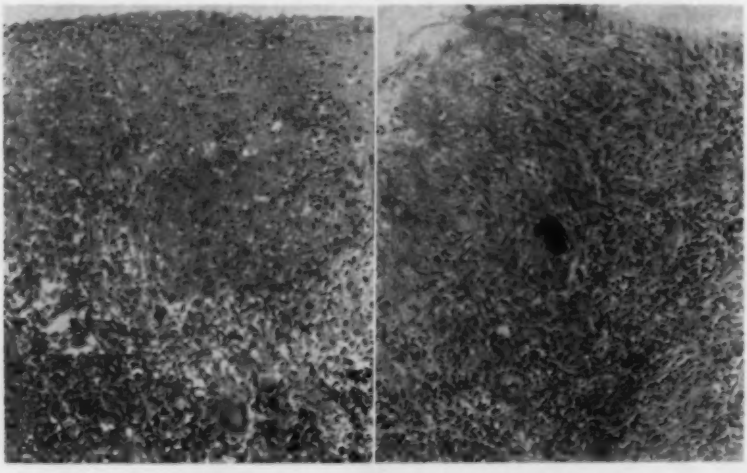

FIGURE 35 FIGURE 36

Figure 35: Higher magnification of section of the caseous wall, showing giant cells and a gradual changing of the caseous pyogenic membrane of polymorphs and monocytes with a residue of lymphocytes and fibroblasts extending towards the inner margin of the cavity wall. X30 H & E.—*Figure 36:* Another view, showing fibroblasts extending towards the edge of the cavity. X30 H & E. Case 33.

cultured, or what exists in other parts of the body after operation is still an open question. The fact remains that no bacilli were demonstrated either in the specimen tested, or in the bronchial secretions.

Likewise the positive smear and culture in 12 specimens and positive culture, with negative smear, in four specimens is only to be expected.

The three positive smears and negative on cultures is not at all unusual. They may have become "lethargic" or actually have reached the death point because of the antimicrobials, but it could have happened naturally.

The pathologic changes were interesting and we believe worthy of the detailed descriptions we have given. We frankly were surprised to find such a high percentage of large cavities that were not only closed, but filled in with fibrous tissue. That is, the "pathologic target point" was reached and they could be classed as completely healed. Others were near to healing. In all but one of these, tubercle bacilli were not found. This one case had only a positive culture. In the two cases without visible cavities, one was positive on smear and another was positive on both smear and culture.

The pathologic changes generally parallel the degree of sterilization of the tubercle bacilli in the organ. In the acute infiltrative types that have not progressed too far, and have not caused the devastating intoxication of the organ with caseation and excavation, the relatively few bacilli are eliminated and the process resorbs much like the clearing of lobar pneumonia. Consolidations may be due to many things. "Infiltrates" may be caused in several ways; by pneumonic process; allergy; atelectasis, or by any other process that causes accumulation of fluid or cellular material in the lungs. The damage done depends upon the amount of tuberculotoxin present in the particular process, which in turn depends on the number of bacilli. The tissue cells are damaged in proportion to the toxic action by tuberculotoxin and perhaps allergy. The epithelium and parenchymatous cells are damaged first, then come circulating blood and lymph cells and last the connective, reticular and elastic tissue. Although the elastic tissue is not at first destroyed, its elasticity is impaired or destroyed to such a degree that varying grades of emphysema result. This has been called by Sweany the "emphysema of healing." It is due to a loss of function of the elastic tissue so that it is unable to regain its normal position after constant stretching during normal or forced respiration. Practically all tuberculous lesions that have cleared show some degree of this emphysema.

In cases with tuberculous pneumonia, destruction of the tissues has progressed much further and in places there is softening and excavation. In these specimens there are usually a larger number of tubercle bacilli and the time element is much longer than in the early tuberculous infiltrations.

In more chronic cases there are varying degrees of healing as shown by proliferation of fibrous tissue, carnified lung tissue and heavier cavity walls.

Re-epithelialization was only observed in one or two specimens. Had each bronchus been studied, especially at its entrance into the cavity, there would, no doubt, have been more cases found as Auerbach has shown. In large, recently excavated cavities, however, there has not been time enough for epithelium to proliferate. This is probably a good thing because the presence of epithelium would tend to, if not actually prevent, a closure of the cavity. In the closed cavities there was no sign of epithelium.

The cases with "open" cavities were practically all positive on culture and some on smear. Enclosed masses or tubercles and cavities were frequently negative. This result was of no practical importance, because the caseous masses are always a threat and had every particle been examined, bacilli may have been found. Besides, the caseous or fibrocaseous masses were a liability from mechanical reasons alone. Soft, caseous masses, or empty cavities are subject to abscess development later.

There is an important lesson from this work and that is that the specimen and even the sputum does not need to be negative to obtain a good surgical result. The principal criterion is the clinical condition of the patient with an advance of favorable factors to, or near the clinical and x-ray film "target point." Of the cases discharged as arrested, 14 had positive cultures in the specimens and only three had positive smears with negative cultures. Of 15 specimens totally negative on bacteriological examination, 14 were discharged as arrested exactly the same number with positive bacterial findings. Of the three fatal cases, one was entirely negative and two were completely positive.

Another important lesson is that there are approximately 25 per cent of ulcerative, moderately advanced and far advanced cases treated with antimicrobials and rest, and brought up for surgery, will recover without surgery at all. Although these cases may not have needed excisional surgery for recovery, there is a finality of surgery that helps to convince everyone that there are no dangerous residues remaining. The assurance to both patient and physician is of much value. If mortality can be kept to near zero, it is a great morale builder and a time saver in most cases.

It will be in order at this point to attempt a breakdown of admissions in an average tuberculosis hospital with respect to the number of cases that are amenable to surgery. Some hospitals still have a majority of far-advanced cases, others have "come nearer to the bottom of the barrel" of the material and admit more early cases. Depending upon the admission policy, therefore, the figures for patients not needing any consideration of surgery varies between rather wide limits with an average perhaps around 50 per cent. This group will respond to rest and drugs alone. The other 50 per cent are sufficiently far advanced to be considered for surgery, after short or long courses of antimicrobials. Some cases may take many months and even years to clear up sufficiently on one side, or in two or even three lobes for operations on the remaining side or lobes.

From the group of cases analyzed in this study and which are fairly

representative of our surgical philosophy at this time, it appears that approximately 15 to 20 per cent of all cases, or 30 to 40 per cent of those cases selected for surgery might subsequently recover without surgical intervention. On the other hand, 15 to 20 per cent of all cases depend entirely upon surgery for eventual salvation if they can be salvaged at all. The remaining cases, variable in each hospital, will in time die of old age, complications (as cancer, heart disease, mental disease, etc.,) or advanced tuberculosis. While all cases were discharged as arrested, it will take 5 years to be certain.

SUMMARY

1. A pathologic and bacteriologic report has been made on resected specimens from 34 patients who received some form of pulmonary resection. One advanced case was included that did not receive surgery, but received antimicrobial therapy.

2. The most important observation was that rest and antimicrobial therapy not only clears up infiltrations in tuberculous cases, but allows the healing of over 25 per cent of recently developed advanced cases by filling in the cavities with granulation tissue and fibrosis, leaving only stellate scars. This group actually does not need surgery, except as assurance to remove any doubts in the minds of the physician, and give satisfaction to the patient. It will give him a shorter convalescence and protect him against any possibility of recurrence of his disease.

3. Another 10-15 per cent may recover without surgery, but for many valid reasons given before, surgery is advisable.

4. The remainder of seriously ill cases (about 60 per cent) need surgery for recovery, if recovery is possible. About half of these are sent home within six months to a year's time after operation as arrested. This group includes more chronic disease where fibrous adhesions and thick walled cavities prevent the closure of cavities. The other cases of this group represent salvage cases, some of which may be prepared for surgery over longer intervals and ultimately operated on; others belong to the various complications; others are too old; while there is a residue of advanced chronics who have little prospect of ever recovering and who will pass away over the years to come.

5. The bacteriologic findings were not unusual. Only three cases were found where there was a positive smear with negative culture. There were 15 negative and 16 positive cultures made from the resected specimens.

6. The various pathologic changes have been discussed.

RESUMEN

1. Se presenta una información patológica y bacteriológica de 34 enfermos a quienes se hizo algún tipo de resección. Se incluye un caso avanzado que no se sujetó a la cirugía, pero recibió terapia antimicrobiana.

2. La observación más importante fué que el reposo y la terapia antimicrobiana no sólo limpió las infiltraciones en los casos de tuberculosis, sino que permitieron la curación de más del 25 por ciento de los casos avanzados de reciente evolución llenando las cavidades con tejido de granu-

lación y fibrosis, dejando sólo cicatrices estelares. Este grupo de hecho no necesita cirugía excepto como un modo de asegurarse y quitar toda duda al médico y dar satisfacción al enfermo. Esto le proporcionará convalescencia más breve y protección contra recurrencia de la enfermedad.

3. Otro 10 a 15 por ciento puede recuperarse sin la cirugía, pero por muchas razones válidas ya dadas, sería la cirugía aconsejable.

4. El resto de los enfermos seriamente enfermos (alrededor del 60 por ciento) necesitan cirugía para recuperarse si es posible.

Alrededor de la mitad de estos son enviados a sus hogares dentro de 6 meses a un año después de la operación, clasificados como detenidos. Este grupo incluye enfermedad más crónica donde las adherencias fibrosas y cavidades de paredes gruesas impiden el cirre de cavidades.

Los otros enfermos de este grupo representan casos de rescate algunos de los cuales pueden ser preparados para cirugía por intervalos largos y después operados; otros corresponden a varias complicaciones; otro grupo es de demasiado viejos y hay un resíduo de crónicos avanzados que tienen muy pocas probabilidades de recuperarse y que morirán en los años venideros.

5. Los hallazgos bacteriológicos no son inusitados. Sólo tres casos se encontraron en los que había un frotis positivo con cultivo negativo. Hubo 15 negativos y 16 positivos al cultivo con material tomado de las piezas resecadas.

6. Se discuten los aspectos anatomopatológicos diversos encontrados.

RESUME

1. Les auteurs rapportent l'examen anatomo-pathologique et bactériologique des pièces opératoires provenant de 34 malades, qui subirent une résection pulmonaire. Ils y ont ajouté le cas d'un malade porteur de lésions très graves qui ne subit pas d'intervention mais reçut une thérapeutique antimicrobienne.

2. La constatation la plus importante fut que le repos et la thérapeutique antimicrobienne non seulement permettent d'effacer les infiltrations tuberculeuses, mais amènent la guérison de plus de 25% des cas de tuberculose d'apparition récente en comblant les cavités de tissu de calcification, et de fibrose, laissant seulement une cicatrice étoilée. Ce groupe de malades n'a pas besoin actuellement d'intervention chirurgicale, à moins qu'on ne veuille enlever tout doute dans l'esprit du médecin et donner satisfaction au malade. Cela lui permettra une convalescence plus courte, et le protégera contre toute possibilité de rechute de la maladie.

3. Un autre groupe de 10 à 15% des malades peut guérir sans intervention, mais pour beaucoup de raisons des plus solides qui ont été énoncées auparavant, la chirurgie est souvent souhaitable.

4. Le reste des malades (environ 60%) comprenant les formes sévères doit être soumis à la chirurgie pour guérir si la guérison est possible. Environ la moitié d'entre eux peuvent être renvoyés à leur domicile dans un délai de 6 mois à un an après l'intervention. Ce groupe comprend surtout des malades chroniques, avec lésions fibreuses et cavités à parois

épaisses empêchant leur fermeture. Les autres cas de ce groupe représentent des cas rebelles, et quelques-uns d'entre eux peuvent être opérés après une préparation plus longuement poursuivie au terme de laquelle l'intervention est devenue possible. D'autres présentent des complications diverses. D'autres sont trop âgés. Enfin, il y a quelques chroniques gravement atteints, qui ont peu d'espoir de jamais guérir, et qui décèderont dans les années à venir.

5. Les constatations bactériologiques furent inhabituelles. Ce n'est que dans trois cas que l'examen sur lame se montra positif alors que les cultures restaient négatives. Il y eut 15 cultures négatives et 16 cultures positives à partir des pièces résectées.

6. Les auteurs mettent en discussion les différentes altérations anatomopathologiques qu'ils ont constatées.

ZUSAMMENFASSUNG

1. Ein pathologischer und bakteriologischer Untersuchungsbefund wurde vorgelegt über Resektionspräparate von 34 Kranken die irgend eine Form von Lungenresektion bekommen hatten. Ein fortgeschrittener Fall wurde einbezogen, der keine chirurgische, wohl aber antimikrobielle Therapie erhalten hatte.

2. Die wichtigste Beobachtung bestand darin, dass Ruhe und antimikrobielle Therapie nicht nur zur Beseitigung von Infiltrationen bei tuberkulösen Fällen führen, sondern auch die Heilung von über 25% von kürzlich entstandenen fortgeschrittenen Fällen ermöglichten durch Auffüllung der Cavernen mit Granulationsgewebe und Fibrose lediglich unter Zurücklassung von sternförmigen Narben. Diese Gruppe benötigt tatsächlich keine chirurgischen Eingriffe ausser als Sicherheit, um jeden Zweifel in der Meinung des Arztes zu beseitigen und dem Kranken Gewissheit zu geben. Der Eingriff ermöglicht ihm eine kürzere Wiedergesundung und schützt ihn gegen jede Möglichkeit eines Rückfalles seiner Krankheit.

3. Weitere 10-15% können sich ohne Eingriffe erholen, aber aus vielen triftigen zuvor aufgeführten Gründen ist der Eingriff anzuraten.

4. Der Rest von schwereren Krankheitsfällen (ungefähr 60%) braucht zur Genesung chirurgische Behandlung, wenn eine Besserung möglich ist. Ungefähr die Hälfte von ihnen werden innerhalb einer Zeit von 6 Monaten nach der Operation als zum Stillstand neigend nach Hause entlassen. Diese Gruppe umfasst mehr chronische Krankheiten, bei denen fibröse Verwachsungen und dickwandige Cavernen den Schluss der Cavernen verhindern. Die anderen Fälle dieser Gruppe stellen Betreuungsfälle dar, von denen einige auf chirurgische Massnahmen auf längere Sicht vorbereitet und später operiert werden können; andere gehören zu den verschiedenen Komplikationen; andere sind zu indolent. Es bleibt ein Rest von fortgeschrittenen chronischen Fällen, die wenig Anwartschaft darauf haben, jemals wieder hergestellt zu werden, und die im Verlauf der Jahre dahinscheiden werden.

5. Die bakteriologischen Befunde waren nicht ungewöhnlich. Es wurden nur 3 Fälle gefunden, bei denen ein positiver Ausstrich zusammen mit

einer negativen Kultur vorkam. Es ergaben sich 15 negative und 16 positive Kulturen bei der Verarbeitung der Resektionspräparate.

6. Die verschiedenen pathologischen Veränderungen werden besprochen.

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The Responsibility of the General Thoracic Surgeon in Cardiac Surgery*

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While pioneering attempts were made in the 1920's to open a stenotic mitral valve, modern cardiac surgery actually began early in the 1940's with the classical investigations of Crafoord, Gross, and Blalock on the treatment of certain types of congenital heart disease. This was followed in 1946 and 1947 by Bailey and by Harken who independently demonstrated the feasibility of successful intracardiac operations. These observations were made in university clinics adequately staffed with trained personnel and supported by appropriate research and laboratory facilities.

In such scientific surroundings, the physiology for, and technique of cardiac operations were properly established. After painstaking laboratory experimentation by these and other pioneers, followed by clinical confirmation of the principles involved, *certain* procedures were proved surgically sound. Subsequently, it was recognized that these cardiac operations could be safely performed by trained thoracic surgeons without the support of the special facilities available only in university centers.

The purpose of this communication is to discuss those cardiac operations which can be performed by the general thoracic surgeon in the well equipped non-university general hospital and to present certain principles which must govern such surgery. The term "general thoracic surgeon" applies to the specialist whose background in thoracic training has qualified him in the surgical management of chest disease. In acquiring such training, he has necessarily accumulated experience in the anatomy and basic physiology of the heart to justify his adoption of established cardiac operative procedures. However, the fact that such operations must be pioneered and well established in university centers cannot be overemphasized.

Probably the most important principle in cardiac surgery is the dependence in this new field upon what we call the team effort: The sum total of the talents of the internist, the surgeon and the anesthesiologist. The proper functioning of such a team begins with the internist who accurately determines the type and extent of the cardiac lesion and the physiologic status of the patient. In consultation with the internist and the anesthesiologist, the surgeon carefully plans the anticipated procedure,

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and during operation each member of the team is responsible for a certain segment of care. The surgeon makes the anatomical corrections, and the internist affords cardiac support and treats the various complications of arrhythmia and hypotension as they may appear. The anesthesiologist produces the necessary degree of anesthesia with the least cardiovascular depression and the best possible degree of oxygenation. Postoperatively, the surgeon and internist combine efforts to carry the patient through the critical period well into convalescence.

Cardiac surgery, performed under conditions as outlined above, may be divided into the following classifications:

A. CONGENITAL LESIONS

1. *Commonly operated*
   Patent ductus arteriosus
   Coarctation of the aorta
   Pure pulmonic stenosis
   Tetralogy of Fallot
   Vascular rings
2. *Rarely operated, or in investigative stage*
   Interatrial septal defects (surgical closures increasing)
   Interventricular septal defects
   Truncus arteriosus
   Transposition of great vessels.

B. ACQUIRED LESIONS

1. *Commonly operated*
   Chronic constrictive pericarditis
   Mitral stenosis
2. *Rarely operated and/or still in investigative stage*
   Coronary artery disease
   Aortic stenosis
   Tricuspid stenosis
   Mitral regurgitation
   Aortic regurgitation
   Tricuspid regurgitation.

It has been our experience that the cardiac lesions designated above as "commonly operated" are readily capable of surgical correction by the general thoracic surgeon with ancillary medical support in well equipped general hospitals.

Congenital Lesions

Lesions such as patent ductus, coarctation, and vascular rings are in general readily defined by the internist utilizing the basic principles of careful history and physical examination, including the electrocardiogram, fluoroscopy and chest x-rays.

From a surgical standpoint, patent ductus presents no problem. In our experience, division of the vessel with direct suture closure has been the standard procedure and has proved entirely satisfactory. However, warning should be given regarding the dangers of division of a patent ductus in which there is pulmonary hypertension *and* a reversal of blood flow with right to left shunt. These cases may be clinically suspected by electrocardiographic evidence of right ventricular hypertrophy, but exact diagnosis of the right to left shunt must be made by arterial oxygen content studies as described by Hultgren, et al.[1] Surgical division in this condition may lead to fatal results. On the other hand, pulmonary hypertension, *per se*, is *not* a contraindication to division if the shunt remains predominantly left to right. When in doubt a simple test at operation is to measure pressures in the pulmonary artery and aorta, prior to and immediately following temporary occlusion of the ductus. In a case favorable for division (left to right shunt) the pulmonary artery pressure diminishes and the aortic pressure increases. After temporary occlusion in unfavorable cases (right to left shunt) the pulmonary artery pressure rises and the aortic pressure falls.[16]

Coarctation of the aorta is diagnosed by simple measures in the majority of cases. An angiogram occasionally may be necessary for final definition. An aortic homograft is rarely necessary in establishing a tension-free vascular channel, but it is advisable to have such a prosthesis available. A graft may be essential in the age group past adolescence (because of precocious aortic atherosclerosis) and in certain instances of infantile or preductal coarctation with an elongated funnel type of constriction. Artery banks providing such material are now being established in greater numbers throughout the country and should be considered as a community project in any area where cardiac surgery is being performed.

Lesions such as Tetralogy of Fallot, pure pulmonic stenosis, and septal defects often may be diagnosed presumptively by careful examination, but frequently require cardiac catheterization and/or angiography for final decision. The surgeon must strive for an exact preoperative diagnosis in every instance because the hazards of exploratory cardiac operations preclude their frequent use in a general hospital.[2, 17]

To go into the details of diagnosis of the cardiac lesions noted above is beyond the scope of this presentation and the reader is referred to more complete treatises on the subject.[3, 4]

The closure of interatrial septal defects has been successfully accomplished by several differing techniques none of which interrupt blood flow through the heart. Interventricular septal defects are, however, another matter and in general their successful closure can only be performed at open cardiotomy. This in turn must await the experimental perfection either of safe hypothermia, or extra corporeal shunts with bypass pumps, oxygenators, or cross circulation maneuvers.[5, 6] Obviously, therefore, it is not yet feasible to attempt the correction of interventricular septal defects in the non-university general hospital.

Acquired Lesions

Chronic Constrictive Pericarditis

The diagnostic evaluation of this lesion and the corrective surgical procedures have been well established. There is no reason to deny surgery to any individual presenting the classical signs and symptoms of cardiac constriction. Local preference dictates the incision and we have in most cases used the transverse bipleural approach. The thorough removal of the entire thickness of pericardium has seemed to us most important in obtaining good clinical improvement.

Mitral Stenosis

Mitral commissurotomy is probably the most frequently performed intracardiac operation at the present time. The beneficial results of this operation are well substantiated when the mitral valve is found to be tightly closed and there is little or no insufficiency.

The determination of "tight" mitral stenosis with a valve opening of significantly less than one square centimeter generally depends upon finding clinical and laboratory evidences of pulmonary hypertension[7] in addition to the typical murmur. Our experience with complete diagnostic evaluation, confirmed by operative findings, has lead us to adopt the following criteria, generally in the order named:

Criteria for Tight Mitral Stenosis

1. History of hemoptysis in which pulmonary infarctation can be excluded.
2. Electrocardiographic evidence of right ventricular hypertrophy.
3. Absent or minimal systolic murmur.
4. Greatly accentuated or reduplicated pulmonic second sound or both.
5. Right precordial heave.[8]
6. Radiologic evidence of marked enlargement of the right ventricular outflow tract.
7. Radiologic evidence of right ventricular enlargement.
8. Slight to moderate enlargement of the left auricle.

In many instances, mitral stenosis is associated with variable degrees of regurgitation. In certain of these cases, especially where regurgitation is significant, mitral commissurotomy may not be indicated since satisfactory procedures are not presently available for surgical correction of the regurgitant problem. Our criteria for determination of significant or predominant regurgitation of the mitral valve are as follows:

Criteria for Predominant Mitral Regurgitation

1. Long and loud systolic apical murmur.
2. Greatly enlarged ("giant") left auricle.
3. Absence of accentuated or reduplicated pulmonic second sound.
4. Electrocardiographic evidence of early left ventricular hypertrophy.[9]
5. Radiologic evidence of left ventricular hypertrophy.
6. Systolic expansion of left auricle by fluoroscopic study.

It should be noted that these criteria, both for tightly closed mitral stenosis and for mitral regurgitation, do not all necessarily apply in each case. The findings may be variable and while their relative importance may be considered in the order named, it is necessary at times to consider all the various diagnostic requirements before a decision may be reached. Our experience would warrant emphasis of the following points.

1. The findings of electrocardiographic right ventricular hypertrophy, hemoptysis without pulmonary infarction, or both, have invariably led to the finding of a tightly closed mitral valve.

2. Significant mitral regurgitation has never been found at operation in the absence of mitral systolic murmur.

The contra-indications for mitral commissurotomy have been well outlined. They are as follows:

Absolute Contra-Indications for Mitral Commissurotomy

1. Active rheumatic heart disease.
2. Subacute bacterial endocarditis.
3. Aortic valve disease with left ventricular hypertrophy.
4. Significant mitral regurgitation, especially when associated with left ventricular hypertrophy.
5. Tricuspid insufficiency.
6. Advanced age, although this factor seems to be diminishing in importance since we have now successfully operated on patients over 60.
7. Associated degenerative disease such as arteriosclerosis, hypertension, asthma, and other debilitating diseases.
8. Chronic long standing auricular fibrillation with hypotension.
9. Any combination of trivalvular disease.

One may also list *relative* contra-indications to mitral commissurotomy: Aortic valve disease, particularly insufficiency without left ventricular hypertrophy; tricuspid stenosis; marked calcification (radiologic) of mitral valve. Under limited circumstances mitral commissurotomy may still be done in the presence of these lesions, but the over-all results will be inferior.

The final factor in selection of patients for mitral commissurotomy depends upon the physiologic status of the patient. A classification[10] for surgical purposes may be defined as follows:

Surgical Classification of Mitral Stenosis

Group I: Benign course—heart murmur only, in a patient who is asymptomatic.

Group II: Static course—slight to moderate symptoms of cardiac inadequacy without progression.

Group III: Progressive disability — increasingly severe symptoms of cardiac inadequacy or actual failure.

Group IV: Terminal group — completely incapacitated, usually with evidences of right ventricular failure (chronically elevated venous pressure, greatly enlarged liver, and marked edema).

With respect to the above classification, it is clear that Group I patients do not need the operation. In Group II, the decision may be difficult and will depend primarily on the degree of constriction of the mitral valve. In those patients with obvious and prominent cardiac enlargement or those in the fifth decade of life, operation will be of benefit. On the other hand, if the patient's cardiac inadequacy is well handled by the usual measures in the third and fourth decade of life and there is little cardiac enlargement, his interest is probably best served by postponement of surgery until a later date. The operation is most desirable in Group III. Group IV patients should be operated upon with full realization of the high operative mortality. The surgeon deals with this group only when he develops increasing experience in the field.

The surgical techniques employed by us in the attack on the stenotic mitral valve are essentially as originally outlined. In over 200 cases subjected to mitral commissurotomy, we have used finger fracture as the sole technique at least 80 per cent of the time. Resistant scars or extensive calcification in the remaining patients have necessitated the addition of directed knife incision. In no instance has the valve only been dilated.

Other Acquired Lesions

Operative procedures for the correction of mitral regurgitation, aortic stenosis and regurgitation, tricuspid stenosis and regurgitation, and improvement of cardiac circulation in coronary artery disease are either in the investigative stage, of questionable value, or technically impossible. Consequently, these procedures do not lend themselves at this time for operation by the general thoracic surgeon.

Care of the Patient Through Cardiac Surgery

The following comments as generally outlined by Black and Harken[11] may serve as guiding principles for carrying the patient through cardiac surgery. They apply particularly to those operations which offer considerable insult to the patient's heart, but may serve for all types of cardiac surgery.

Preoperative Period

If a patient is in borderline cardiac failure, it is mandatory that the internist member of the team spend two, four or even six weeks in working out a regimen of medical cardiac care which will bring the patient to the operating room in optimum condition. Hospitalization during a portion of this period may be advisable. In any event, admission to the hospital should be at least three to four days prior to surgery. During this period, the physiologic status is carefully revaluated and salt restriction is maintained if there is evidence of cardiac inadequacy. Care must be exercised to prevent salt depletion; if there is doubt as to electrolyte

imbalance, chemical determinations of sodium, potassium, and chlorides are made. This will furnish a baseline in order more intelligently to balance electrolytes during the early postoperative period. Mercurial diurectics are administered if necessary.

Where patients are, or have been in cardiac failure they are carefully digitalized. This is especially valuable in patients with auricular fibrillation in order to prevent a rapid cardiac rate. Unless a patient with auricular fibrillation has already been converted to normal sinus rhythm, the use of quinidine is not employed since it is common experience that reversion to auricular fibrillation usually occurs with manipulation of the heart during surgery.

Surgical Period

Preoperative sedation is held to a minimum. The majority of our patients receive an intravenous sodium pentothal induction, after which they are intubated and carried on nitrous oxide and oxygen, together with small amounts of curare. In instances where this type of anesthesia produces a hypotension of significance with tachycardia (not infrequently seen with chronic auricular fibrillation), or when serious arrhythmias begin before operation is started, we cancel the operation and bring the patient back for surgery several days later. Failure to heed these warning signs was the direct cause of two fatalities in our early experience. At the later operation, we have found that changing over to ether as the anesthetic agent may prevent such complications. We have not found low concentration intravenous procaine solutions, even when administered continuously, to have any significant effect in preventing arrhythmias.

In operations directly upon the heart, an electrocardiographic tracing is recorded, utilizing that lead which best brings out the P waves and QRS complexes, usually lead II. The esophageal lead may be of value. Spot tracings are made until the heart is directly attacked; from this point until cardiac manipulation is finished, a continuous tracing is obtained. Various arrhythmias are seen particularly with mitral commissurotomy,[12, 13] such as scattered or paroxysmal runs of auricular or ventricular ectopic beats, flutter with varying degree of block, auricular fibrillation, ventricular tachycardia, and on rare occasion, even ventricular fibrillation.

The internist must be prepared to treat the serious arrhythmias immediately. Scattered ectopic beats need little or no attention. The appearance of auricular flutter will call for treatment. Persistent ventricular tachycardia is an ominous sign. The internist should have available for immediate use the following: prostigmine for sinus tachycardia, atropine for sinus bradycardia, a rapidly acting preparation of digitalis such as lanatoside C (Cedilanid) for flutter, and either Pronestyl or quinidine for ventricular tachycardia.

The appearance of cardiac standstill or ventricular fibrillation calls for the immediate activation of a predetermined plan. Here the surgeon plays the important role with advice from the internist who is monitoring the procedure via the electrocardiogram. First and foremost, anoxia must be corrected. It is the responsibility of the anesthesiologist to maintain

high oxygen concentrations and give assurance of a completely open airway. If standstill is the problem rhythmic cardiac compression and intracardiac epinephrine are usually successful. Feeble beats can be strengthened by the use of 10 per cent calcium chloride injected directly into the left auricle. Limited experience with the pace maker suggests that it, too, may be of value.

If ventricular fibrillation occurs, rhythmic cardiac compression is *still* the first treatment of choice. The aorta should be occluded by finger pressure just distal to the left subclavian artery. Procaine may be injected directly into the ventricle. These maneuvers are frequently successful in causing standstill. Continued rhythmic cardiac compression will then restore normal rhythm. While it is important not to place sole dependence on the defibrillator, this device should be employed shortly if cardiac "massage" is not successful.

The appearance of sustained hypotension calls for the use of any of the pressor agents, of which none seems to have any significant advantage over the others. It has been our practice first to employ small repeated doses of Wyamine or Vasoxyl intravenously. If these agents do not sustain the blood pressure, we then switch to a continuous drip of Levophed solution. Generally we dislike to use the last agent since it takes 12 to 24 postoperative hours to "wean" the patient from Levophed, but there is no doubt of its efficacy in sustaining blood pressure.

Postoperative Period

Following surgery, the patient is taken to the recovery room where careful observations are made by the anesthesiologist, the internist, the surgeon and specially trained nurses. When reacting fully with sustained blood pressure, the patient is returned to his room under the direct care of selected special nurses who are retained until the third or fourth postoperative day.

During the first 24 hours, intravenous fluids are generally necessary and it has been our practice to administer 1500-2000 cc. of five per cent glucose in water, with approximately 4.5 grams (or less) of sodium chloride.[15] If there is any doubt as to electrolyte balance, free use of chemical determination of sodium and chlorides are made. Soluble digitalis products in appropriate amount are added to this solution if needed, particularly if the patient has auricular fibrillation with rapid ventricular rate. In the early postoperative period there is generally water retention, but about the third postoperative day, there is usually a relative diuresis lasting approximately 24 hours.

If the patient is fibrillating, attempts at conversion should be made as early as possible in the postoperative period to insure a maximum cardiac output. This may be done within the first two postoperative days if the ventricular rate is not well controlled with digitalis. On the other hand, if the ventricular rate is maintained at a relatively slow rate, attempts at conversion are best made about the fourth or fifth postoperative day with quinidine by mouth at which time the patient is accepting a full diet

and taking adequate fluids. Such early conversion of auricular fibrillation is physiologically sound.

The average patient is made relatively comfortable with 50 mg. doses of Demerol, usually at three to four hour intervals. Morphine is rarely used because of respiratory depression.

Patients usually begin sitting over the side of the bed by the third or fourth day, are placed in a chair by the fifth or sixth day, and are ambulating by the seventh or eighth day.

Aqueous procaine penicillin is administered prophylactically beginning on the day before operation through the seventh or eighth day in a dosage of 600,000 units per day to prevent the development of bacterial endocarditis.

From time to time, patients are seen with an inordinate amount of chest pain in the postoperative period. This pain is usually over the precordium, non-radiating, and is increased by respiration. It generally begins about the third postoperative day and may continue out through the ninth or tenth day and sometimes even longer. Its etiology is not clear. On the basis that this pain may possibly be an activation of a rheumatic process, Cortisone has been judiciously administered in a few cases with apparent relief.

Present Trends in Cardiac Surgery in A Non-University General Hospital

It has been emphasized in preceding sections of this report that it is perfectly proper for the general thoracic surgeon to perform certain standard cardiac operations in a well equipped general hospital. In the main, these are operations for cardiac or vascular lesions which are capable of being diagnosed by the commonly available methods in physical diagnosis, radiology, and electrocardiography. Therefore, the operations are pretty much limited to the correction of six or seven conditions when they exist in uncomplicated form: Persistent patent ductus arteriosus, coarctation, vascular rings, Tetralogy of Fallot, pulmonary valvular stenosis, chronic constrictive pericarditis, and mitral stenosis.

Atypical examples of usually simple abnormalities (the occasional ductus), more complicated lesions, and combined lesions almost always must be diagnosed by special means. This necessitates sending the patient to a special diagnostic center. Following such diagnosis, one wonders whether many of these patients should not have their surgery also at a center. One good reason in certain instances would be the necessity for obtaining accurate intracardiac pressures during operation by means of equipment not usually available in most general hospitals.

A present, and apparently a proper trend, is the development of special diagnostic centers in metropolitan areas not immediately in contact with a university hospital. This would seem logical because even highly technical diagnostic procedures are now becoming standardized. Certain criteria are necessary. The entire interested group in any community should

decide where such a center is to be located. If only because of the expense involved, it would not seem feasible to set up competing laboratories.

Until recently, these non-university centers have been extremely rare in the United States. It can now be reported that such a center, The East Bay Cardio-Respiratory Center at Samuel Merritt Hospital in Oakland, California, has now been in operation for more than a year. Merritt Hospital was chosen after prolonged study. It seemed the most logical location because the hospital was equipped by the availability of staff funds, by the possession of the proper contracts and by basic philosophy to handle all types of patients: Private, clinic, indigent, veterans, Crippled Children Service and Vocational Rehabilitation patients. Again we should emphasize this Center as a community project. Money for its establishment came from various sources: The Trustees at Merritt Hospital; the Alameda County Heart Association; private donations of patients and of physicians.

The laboratory is under the direction of Dr. Charles A. Webster who is in private practice and who is trained in catheterization and in respiratory function studies. The professional activities are reviewed by a committee composed of internists, radiologists, thoracic surgeons, physician representatives of the Heart Association, and physician representatives of the Hospital.

The scope of this paper permits only an outline of the services available: Cardiac catheterization with special electronic devices for the permanent recording of pressure measurements; a cuvette oximeter; and laboratory facilities for accurate oxygen determination. There are radiologic facilities for angiocardiography as well as for retrograde aortagrams. Apparatus is available for the more complicated as well as the routine respiratory function studies. The combination of facilities for special cardiac diagnosis and for respiratory tests seems a happy one. At the time of a cardiac operation, facilities are available for the accurate measurement of intracardiac pressures with simultaneous electrocardiograms, and also for instantaneous oxygen saturation studies should these be desired.

An important concomitant is the recent establishment of a homograft tissue bank in a nearby clinical laboratory. This is also a community project. Money for the freeze drying equipment was donated by the local Heart Association. Freeze-dried vessels are now available both for thoracic surgeons as well as for those performing general vascular surgery. When other freeze-dried tissues (for example dura and fascia) are proved satisfactory, these can easily be stored in the bank.

As a result of these efforts and of the teamwork of all concerned, more and more complicated cardiac procedures are being undertaken as soon as laboratory and clinical proof of their soundness has been obtained.

Finally, it must be re-emphasized that the laboratory facilities as just described are not *primarily* designed for pioneering advances nor for basic research, although they can easily be used for clinical investigation. The present trend in cardiac surgery as we see it contemplates some decentralization as far as university centers are concerned. As a logical

sequel in certain communities there is thus encouraged the establishment of special diagnostic facilities to complement the ever widening horizon of cardiac surgical endeavor.

SUMMARY

Cardiac and intrathoracic vascular surgery has arrived at the point where certain established operations may be safely carried out by the general thoracic surgeon in a non-university hospital. The medical responsibility for the proper handling of such operations is shared equally by internist, surgeon, and anesthesiologist.

Accurate preoperative diagnosis is essential to the proper management of the individual case in order for the operating surgeon to be sure that he will be able to carry out a technique previously proved to be generally effective.

Diagnostic problems of any sort must be referred to cardiac catheterization laboratories whose function it is to clarify difficult and complicated situations. Exploratory cardiotomy as well as new operations whose techniques are still under investigation should not be performed in other than fully equipped centers.

A present trend is the development in certain metropolitan areas of completely equipped cardiac diagnostic and surgical facilities which are not directly connected with university hospitals. Presumably the number of such centers will remain small because of the limitations of expense and the necessity for highly trained personnel. Their establishment seems logical, however, provided that each center remains an integrated community project.

The functioning of such a laboratory, the East Bay Cardio-Respiratory Center, has been briefly described.

RESUMEN

La cirugía vascular y cardiaca han llegado a un punto tal que ciertas operaciones pueden llevarse a cabo con seguridad en un hospital no universitario por un cirujano general de tórax.

La responsabilidad por la apropiada técnica en tales operaciones es compartida por el internista, el cirujano y el anestesista por igual.

Es esencial que haya un diagnóstico preoperatorio exacto para que el tratamiento sea adecuado a fin de que el cirujano lleve a cabo una intervención cuya efectividad ya se haya probado.

Los problemas de diagnóstico de cualquier naturaleza deben ser pasados a los laboratorios de cateterización cardiaca para aclarar los casos difíciles. La cardiotomía exploradora así como las nuevas operaciones cuyas técnicas aún están bajo investigación no deben llevrase a cabo sino por los centros completamente equipados.

La tendencia actual es el desarrollo en ciertas áreas de las grandes capitales de equipos completos para el diagnóstico y el tratamiento quirúrgico con facilidades sin que estén en conexión conlos hospitales universitarios. Es de esperarse que el número de tales centros será pequeño por las limi-

taciones impuestas por los gastos y la necesidad de personal altamente adiestrado. Su creación parece lógica sin embargo, siempre que cada centro permanezca formando parte de un programa de la comunidad.

La función de tal laboratorio, el Centro Cardiorespiratorio East Bay, se ha descrito brevemente.

RESUME

La chirurgie vasculaire cardiaque et intrathoracique est arrivée à un tel point de perfection que certaines opérations bien mises au point peuvent être tentées sans danger par le chirurgien de chirurgie thoracique générale dans un hôpital non universitaire. La responsabilité médicale pour la réussite de telles opérations est partagée par le médecin, le chirurgien et l'anesthésiste.

Un diagnostic précis avant l'opération est essentiel pour la préparation de chaque cas, de façon à ce que le chirurgien soit assuré de pouvoir mener à bien une technique qui s'est révélée auparavant généralement efficace.

Les problèmes diagnostiques de toute sorte doivent être étudiés au laboratoire de cathétérisme cardiaque, dont la fonction est d'éclaircir les cas difficiles, et compliqués. La cardiotomie exploratrice de même que les nouvelles opérations dont les techniques sont encore à l'étude de devraient être pratiquées que dans des centres parfaitement équipés.

La tendance actuelle dans certains grands centres urbains est de développer des moyens de diagnostic cardiaque perfectionné et des facilités chirurgicales sans faire appel aux hôpitaux universitaires. Les auteurs supposent que de telles institutions resteront peu nombreuses, à cause des limites apportées par leur coût, et par la nécessité d'un personnel hautement qualifié. Leur installation semble logique à condition toutefois que chaque centre reste intégré à la communauté.

Les auteurs font la description succinte d'un tel laboratoire: le Centre Cardio-Respiratoire de East Bay.

ZUSAMMENFASSUNG

Die Chirurgie des Herzens und der intrathorakalen grossen Gefässe hat einen solchen Stand erreicht, dass gewisse bewährte Operationen von allgemeinen Thoraxchirurgen in Nicht-Universitätskrankenhäusern ohne Gefahr ausgeführt werden können. Die medizinische Verantwortung für die einwandfreie Handhabung solcher Operationen wird gleichermassen vom Internisten, vom Chirurgen und Anaesthesisten getragen.

Eine genaue praeoperative Diagnose ist zur richtigen Behandlung jedes einzelnen Falles notwendig, damit der Operateur sicher ist, dass eine Technik angewandt werden kann, die sich als allgemein wirksam bewährt hat.

Diagnostische Probleme jeder Art müssen Herzkatheterisierungslaboratorien übergeben werden, deren Aufgabe es ist, schwierige und komplizierte Fälle aufzuklären. Probekardiotomien oder neue Operationen, deren Technik noch in Erprobung ist, sollten nur in voll ausgerüsteten Zentren durchgeführt werden.

Es besteht zur Zeit die Tendenz, dass in gewissen Grosstädten gut ausgerüstete Einrichtungen zur Herzdiagnostik und zur Thoraxchirurgie

sich entwickeln, die nicht direkt mit den Universitätskliniken verbunden sind. Wahrscheinlich wird die Zahl solcher Zentren klein bleiben wegen den Unkosten und der Notwendigkeit, gut ausgebildetes Personal heranzuziehen. Ihre Einrichtung erscheint jedoch sinnvoll, vorausgesetzt, dass jedes Zentrum der Gemeinde-Verwaltung unterstellt bleibt.

Die Arbeitsweise eines solchen Laboratoriums, des East Bay Cardio-Respiratory Center, wurde kurz beschrieben.

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Pulmonary Changes Occurring in Disseminated Lupus Erythematosus*

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Disseminated lupus erythematosus belongs to that group of disorders to which the term "collagen diseases" has been applied. The collagen diseases are characterized anatomically by generalized alteration of the connective tissue of the body, especially of its extracellular components, and usually involve many organs. Among the better-known members of the collagen disease group are disseminated lupus erythematosus, dermatomyositis, periarteritis nodosa, scleroderma, rheumatoid arthritis and rheumatic fever. Although many interesting hypotheses have been advanced to account for the development of the collagen diseases, their exact etiology has not been definitely established.

Disseminated lupus erythematosus may be defined as a collagen disorder that is characterized by protean manifestations, of which cutaneous eruptions and an arthralgic toxic state with prolonged periods of fever and a remittent cachectic course are prominent features. It is a disease that is seen most frequently in the third and fourth decades of life and that occurs more frequently in women than in men in a ratio of seven to three.

The cutaneous manifestations which are so closely associated with lupus erythematosus may be divided into two types. One is a discoid, benign form with a "butterfly" eruption over the bridge of the nose and the malar prominences. The other is the acute, disseminated form, which has a tendency to spread over the face, ears, arms, chest and, subsequently, virtually all over the body. In the acute disseminated form of lupus erythematosus the visceral symptoms may precede the cutaneous manifestations, which may appear only in the terminal stage of the disease.

The clinical diagnosis of disseminated lupus erythematosus is based on the clinical history of intermittent bouts of prolonged fever, arthralgia associated with toxicity, the presence of L.E. cells in the peripheral blood or bone marrow, and leukopenia with an elevation in the sedimentation rate.

Although pathologists and clinicians have been aware for many years that pulmonary complications are often terminal events in the life history of the patient suffering from disseminated lupus erythematosus, the presence of pulmonary changes of other types appearing at various times throughout the course of the disease is not as well known. Sante and Wyatt[1]

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have expressed the opinion that patients with disseminated lupus erythematosus, scleroderma and dermatomyositis do not manifest pulmonary involvement roentgenographically until the terminal stages of the disease. That pulmonary changes might occur during the course of the disease other than during the terminal stages was pointed out by Osler[2] in 1904. He described a patient with lupus erythematosus in whom lobar pneumonia developed which subsequently cleared despite a protracted course. That pulmonary changes do frequently occur during the course of the disease would seem to be borne out by the roentgenologic observations of Israel[3] and of Garland and Sisson.[4] They reported a high percentage of pulmonary changes as seen on roentgenologic examination of their patients with disseminated lupus erythematosus.

Clinically, pleuropulmonary and cardiac disturbances are frequently encountered in disseminated lupus erythematosus, becoming more prevalent toward the terminal stages of the disease. In the presence of such disturbances the patient is likely to complain of pain in the chest, especially when pleural involvement exists. The pain is usually aggravated by deep inspiration and cough. On auscultation or palpation of the chest a pleural rub can often be detected. Pleural effusion frequently develops and may bring about with it a decrease in the chest pain, but in turn may cause an increasing degree of dyspnea. The pleural changes may or may not be associated with pulmonary consolidation. In the presence of pulmonary involvement a cough with expectoration may develop. The sputum may be clear or blood-tinged and on rare occasions may consist of clear blood. Dyspnea may or may not be present, and may be due to pulmonary consolidation, pleural fluid or cardiac damage. Again, extensive changes may occur in the lungs and be entirely asymptomatic.

One of the most striking features of the pulmonary changes that occur in the lungs in disseminated lupus erythematosus is that they have a tendency to shift from place to place and from one side to another in the lung with surprising rapidity. They may disappear entirely, only to recur weeks or even months later. That they are not always a terminal manifestation of the disease is seen from the fact that they may completely clear before death of the person affected.

The difficulty of determining the exact nature of many of the pulmonary changes during the life of the patient with disseminated lupus erythematosus has been stressed by Klemperer and his associates[5] who very appropriately stated, "The post mortem observations in disseminated lupus erythematosus do not properly reflect the remarkable clinical manifestations of pulmonary involvement in this disease."

In order to better evaluate the changes that occur in the lungs during the life cycle of the patient with disseminated lupus erythematosus, it is necessary to review the information that can be obtained from a study of the various gross and histologic lesions that will be found at necropsy and to attempt to correlate such findings with the roentgenographic changes noted in the lung. That such a study will not reflect the actual conditions that always exist is obvious, but at least it affords a clue to

the possible changes that may take place.

The present study is based on a review of 54 cases of proved disseminated lupus erythematosus seen at the Mayo Clinic from 1925 through 1952 in which necropsy material from the lungs was available for study. No cases were included which did not present the following criteria: (1) a clinical history compatible with the diagnosis of disseminated lupus erythematosus, (2) demonstration of the presence of microscopic visceral lesions in the kidneys, spleen and skin characteristic of the disease, and (3) the presence of the L.E. phenomenon in the peripheral blood or bone marrow of those patients studied since 1948. The group consisted of 47 females varying from 9 to 66 years of age, and seven males ranging from 19 to 54 years of age.

One of us (Purnell), Baggenstoss and Olsen,[6] in a review of the microscopic findings of necropsy material in the 54 cases, found the significant pathologic changes involving the lungs listed in the table, along with their frequency of occurrence.

Bronchopneumonia was the commonest finding and was present in 41 (75.9 per cent) of the necropsies. The pneumonia showed no distinct or unusual histopathologic features as compared to those seen in bronchopneumonia occurring in persons dying from causes other than lupus erythematosus. In most cases the patient had demonstrated a normal leukocyte response to the pneumonia with a count often in excess of 10,000 per cubic millimeter of blood. The response of the pneumonic process to antibiotic therapy had been in most cases similar to that seen in other types of bronchopneumonia.

Ten of the patients showed pathologic evidence of organization of alveolar exudate in restricted areas of the lung. In no instance was marked organization of the exudate with carnification seen. The organization of alveolar exudate in each instance was found where there had been clinical evidence of a terminal respiratory infection.

Twenty-nine (53.7 per cent) of the cases showed evidence of interstitial pneumonia. In 24 of the 29 cases this was diffuse in its distribution and in the remainder it occurred in isolated focal areas. The changes consisted of inflammatory exudates within the substance of the alveolar walls and interstitial connective-tissue septa. In a high percentage of these cases, inflammatory cells and fibrinous exudate could be demonstrated within the alveolar spaces. In most cases the area of involvement was small and it could be recognized grossly in only two instances.

Hemorrhage was found to be present in two thirds of the cases. It varied from small, focal, subpleural, petechial hemorrhages to massive bleeding involving an entire lung, and was a frequent component of the exudate in cases of bronchopneumonia. Although hemorrhage was occasionally observed in conjunction with purpuric areas on the skin and associated with changes in the bleeding and clotting mechanism, in most instances no readily demonstrable etiologic factor was apparent and it was assumed that the bleeding occurred as a result of damage to the capillary walls.

Pleural changes were frequently found, pleural effusion being present in 66.7 per cent of cases. Only cases in which there was a quantity of fluid in excess of 100 cc. were considered as showing pleural effusion. Amounts of fluid in excess of a liter were not unusual. The fluid was usually clear, transparent, and yellow in color, only rarely being turbid or fibrinous. In 23 cases (42.6 per cent) there was evidence of an acute fibrinous pleuritis, and this was found frequently to be associated with evidence of bronchopneumonia. In approximately one third of all cases there was evidence of pleural fibrosis. The association of pleural fibrosis and acute pleuritis was a common occurrence, testifying to multiple episodes of involvement. Although pleural changes were found to be associated with pulmonary consolidation, they did frequently occur without it.

Pulmonary edema was found in 30 cases. Five of these had evidence of cardiac failure and three had evidence of vasomotor collapse. No specific exciting factor could be determined in the majority of cases. Atelectasis of variable degree and extent occurred in 15 cases showing interstitial inflammatory exudates. In nine additional cases there was a focal area of collapse. Although pulmonary congestion was found in over one half of the cases examined, it was impossible to say whether it was an essential feature of the illness or resulted from a long period of remaining in a recumbent position, or was merely an agonal development.

Slightly more than one of every four lungs examined showed an acute purulent bronchitis, the essential features being a mucopurulent exudate containing polymorphonuclear leukocytes within the lumen and infiltrating the bronchial mucosa and submucosa with similar cells. Pulmonary abscesses were found nine times, each time being associated with bronchopneumonia and usually manifested in the form of several small abscesses within an area of pneumonic consolidation. It was surprising that in spite of the frequency of infection and the toxicity of the patient, empyema was found in only two cases.

One of the most interesting observations was the presence of a mucinous edema in nine of the cases, appearing in the connective tissue of the alveolar walls and in perivascular and peribronchial tissues. This is a condition which Baggenstoss[7] has hypothesized may be a precursor of interstitial pneumonitis. We, however, did not find any evidence of fibrinoid degeneration or necrosis in the pulmonary tissues in this series. It is a condition that is not limited to disseminated lupus erythematosus and has been observed in other collagen disorders.

Tuberculosis was found to exist in the lungs in nine of the 54 cases studied, and in three others there was evidence of pulmonary infarction. There were two cases of empyema and two of bronchiectasis with single examples of lobar pneumonia, bronchial adenoma and calcified cyst. It would appear, therefore, that the lungs of the patient with disseminated lupus erythematosus are an excellent soil for the development of pulmonary changes other than those due to lupus alone.

It is obvious that the pathologic changes that occur in the lungs in disseminated lupus erythematosus are variegated in character, are subject

to alterations and changes, and at best are not pathognomonic. To add to the confusion, the changes that do occur in the lungs must be differentiated from those produced by disease or tumor formation that is in no way related to the lupus itself.

How accurately do roentgenograms of the chest reveal the pathologic changes that take place in the cardiorespiratory system in disseminated lupus erythematosus? The accuracy of the roentgenologic findings will depend in large measure on the period during the course of the disease when the roentgenogram of the chest was made. The pulmonary changes in lupus erythematosus being of a waxing-and-waning character, roentgenograms made of the chest during a period of remission in the cycle of the disease might well show essentially nothing of diagnostic import. Pleuropulmonary findings are most prone to develop in the terminal stages of the disease, and consequently roentgenograms of the chest made at this time will show many more changes than those made early in the course of the disease.

In the 54 cases in the present study, roentgenograms of the chest were made in 52 of the cases at some time during the course of the disease. In the two instances in which roentgenograms were not available, the patient was in extremis at the time of admission to the Mayo Clinic and roentgenograms of the chest did not seem indicated. Thirty-four of the 52 patients showed roentgenographic evidence of cardiorespiratory abnormalities. Pneumonia was the most frequent finding and was evident in 12 instances (fig. 1). The pneumonic process did not present any particular significant pattern. It did tend to change rapidly in its appearance. Pleural effusion was noted 10 times (fig. 2) and varied considerably in amount. It likewise had a tendency to appear and disappear rapidly and to shift from side to side. While most cases with pleural effusion showed

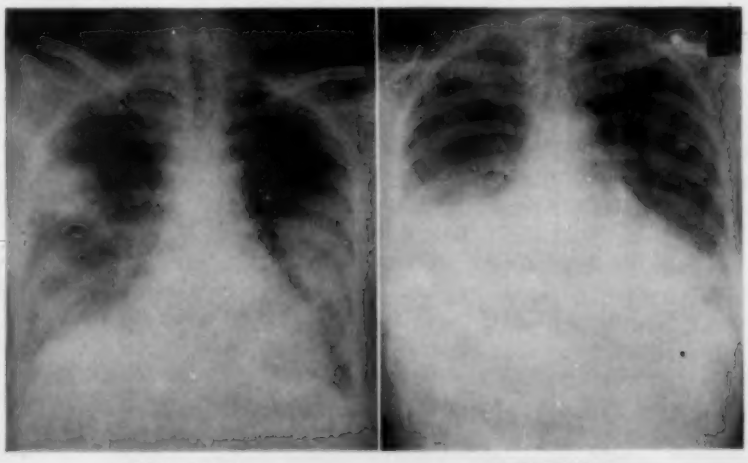

FIGURE 1 FIGURE 2

Figure 1: Bilateral bronchopneumonia in disseminated lupus erythematosus.—*Figure 2:* Fluid in pleural cavity in disseminated lupus erythematosus.

INCIDENCE OF PULMONARY LESIONS IN 54 CASES OF DISSEMINATED LUPUS ERYTHEMATOSUS

Lesions	Cases	Per cent
Bronchopneumonia	41	75.9
Hemorrhage	36	66.7
Pleural effusion	36	66.7
Pulmonary edema	30	55.6
Interstitial pneumonia	29	53.7
Atelectasis	24	44.4
Acute pleuritis	23	42.6
Pleural fibrosis	19	35.2
Acute bronchitis	15	27.8
Organizing pneumonia	10	18.5
Mucinous edema	9	16.7

some evidence of cardiac enlargement, this was not invariably true. In two instances the cardiac silhouette remained within normal limits. In one case with pleural fluid there was evidence of pneumonia as well as of cardiac enlargement. Although cardiac enlargement is generally regarded as a frequent accompaniment of disseminated lupus erythematosus, in our study it was noted as an isolated finding only three times. Pulmonary edema was noted in three cases (fig. 3) and as a rule occurred in the terminal stages of the disease. Nonspecific areas of pulmonary fibrosis (fig. 4) were seen five times. Although such findings should suggest the possibility of lupus, especially in a young woman with an unexplained toxic state, it was almost impossible to distinguish such lesions from small areas of pulmonary infarction, tuberculosis or carcinoma of the lung.

Israel and Garland and Sisson have reported that they found roentgenologic evidence of pulmonary and cardiac abnormalities in a high

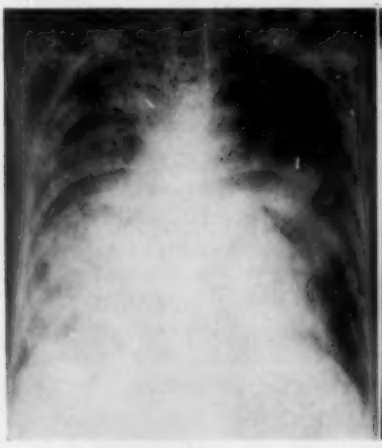

FIGURE 3

FIGURE 4

Figure 3: Pulmonary edema in disseminated lupus erythematosus.—*Figure 4:* Localized fibrous left apex in disseminated lupus erythematosus.

percentage of patients with disseminated lupus erythematosus. Israel found such abnormal pulmonary findings in 17 of 22 patients with the disease; 15 showed evidence of bronchopneumonia and two of pleural effusion. Garland and Sisson found that in 21 of 32 patients with disseminated lupus erythematosus studied by them, the roentgenograms of the chest showed abnormalities. In their group of cases pleural and pericardial effusions were the commonest findings.

It is evident that roentgenograms of the chest in patients with disseminated lupus erythematosus will show evidence of pulmonary and cardiac change very frequently. Undoubtedly, such changes would be even commoner if roentgenograms were made during the last 48 hours of the patient's life. Probably the most striking feature of the roentgenologic changes found in the lungs in this disease is that they do not present any single specific or characteristic picture. When changes are present in the lungs they are subject to rapid and widespread change.

SUMMARY

From the roentgenologist's standpoint, collagen disease and disseminated lupus erythematosus should be considered in the case of any young woman who is suffering from an unexplained toxic state, and whose roentgenogram of the chest shows nonspecific pulmonary changes. A patchy type of pneumonia and pleural effusion, either with or without evidence of enlargement of the cardiac silhouette, are the most prevalent findings.

Disseminated lupus erythematosus does not present a characteristic appearance either on microscopic examination of pulmonary tissue or on roentgenographic examination of the chest. The roentgenographic changes noted in the lungs during the course of the disease do not always accurately reflect the pathologic changes that may be taking place in the lungs. At best, roentgenographic examination reveals that the lungs may be involved in the disease process and that a patient afflicted with disseminated lupus erythematosus is a likely candidate for other types of disease to involve the lungs.

RESUMEN

Desde el punto de vista del roentgenólogo, la enfermedad colágena y el lupus eritematoso deben considerarse en el caso de cualquiera mujer joven que sufra de un estado tóxico inexplicable y cuyo roentgenograma del tórax muestre cambios pulmonares no específicos. Los hayazgos más prevalecientes son un tipo de neumonía moteada y derrame pleural ya sea con evidencia o sin muestra de crecimiento de la silueta cardiaca.

El lupus eritematoso diseminado no presenta un aspecto característico ya sea al examen microscópico del tejido pulmonar o al examen radiológico del tórax. Los cambios roentgenológicos notados en el pulmón durante el curso de la enfermedad no siempre reflejan exactamente los cambios patológicos que pueden tener lugar en el pulmón.

Cuando más un examen radiológico revela que los pulmones se encuentran comprometidos en el proceso pathológico y que el enfermo afectado por el lupus eritematoso diseminado es un posible candidato a otras formas de enfermedad que afectan los pulmones.

RESUME

Du point de vue du radiologiste, la maladie collagène et le lupus érythémateux disséminé devraient être évoqués dans le cas de toute jeune femme souffrant d'un état toxique indéterminé, et dont la radiographie pulmonaire montre des altérations pulmonaires non spécifiques. Des ombres de type pneumonique, un épanchement pleural avec ou sans augmentation de volume de la silhouette cardiaque, sont les constatations essentielles.

Le lupus érythémateux disséminé n'a pas un aspect caractéristique soit à l'examen microscopique du parenchyme pulmonaire soit à l'examen radiographique du poumon. Les modifications radiographiques des poumons notées au cours de l'évolution ne reflètent pas toujours avec précision les modifications anatomo-pathologiques qui peuvent exister au niveau des poumons. Au mieux, l'examen radiographique révèle que les poumons peuvent être atteints par le processus, et que le malade porteur du lupus érythémateux disséminé est un candidat aux autres sortes d'affections qui atteignent les poumons.

ZUSAMMENFASSUNG

Vom röntgenologischen Standpunkt muss eine Bindegewebserkrankung und ein disseminierter lupus erythematosus in Erwägung gezogen werden, im Falle eine junge Frau an einem unklaren toxischen Zustandsbild leidet und ihre Brustkorb-Röntgenaufnahme unspezifische Lungenveränderungen zeigt. Ein unregelmässigfleckiger Typ von Pneumonie und pleuralem Erguss, entweder mit oder ohne Anzeichen von Vergrösserung der Herzumrisse kommen am häufigsten vor.

Der disseminierte lupus erythematosus bietet kein charakteristisches Aussehen, weder bei der mikroskopischen Untersuchung von Lungengewebe, noch bei der röntgenologischen Thorax-Untersuchung. Die im Verlauf der Erkrankung in den Lungen festgestellten röntgenologischen Veränderungen geben nicht immer genau die pathologischen Veränderungen wieder, die in den Lungen stattfinden können. Im besten Falle offenbart die röntgenologische Untersuchung, dass die Lungen in den Krankheitsprozess verwickelt sind und dass ein von einem lupus erythematosus betroffener Patient die Aussicht hat, andere, die Lungen betreffende Krankheitstypen zu bekommen.

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The Selection of Anti-Microbial Drugs for Patients of Different Categories

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The supplementation of the streptomycin-para-aminosalicylic acid combination with isoniazid,[1, 2, 3] a newer, more potent anti-tuberculous chemotherapeutic agent, suggested that the therapy of tuberculosis was at last to be vastly simplified. No prediction has been more untrue or as completely confounded. In place of a simple program consisting of rest and an abundant diet and a medical-surgical regimen solely composed of medical lung collapse and thoracoplasty, we have now to concern ourselves with the proper utilization of almost a dozen antimicrobials of established potency and a like number of surgical procedures. The older standbys are fading from the scene, but the exact roles of the newer modalities, and especially surgery, are still but incompletely understood.

This paper is limited to its assigned task, a discussion of the currently available antimicrobial drugs for the treatment of patients of different categories. A variety of opinions, culled from the literature, will be repeated. Personal observations will be made.

It might be well to first dispose of two groups of compounds for which no great current interest is expressed. The first of these is the sulfone group, the most noteworthy members of which are the diamino diphenylsulfone derivatives, diasone, promine and promizole.[4] They must be deemed failures; the failures are obviously due to toxicity which effectively prevents achievement of the predicted therapeutic range. This field of interest has not been entirely closed, however, and other compounds have been synthesized and studies are being conducted in an effort to harness the acknowledged potency of diamino diphenylsulfone.

The second group for disposal is that of the thiosemicarbazones.[5] Of limited activity and high toxicity, the usefulness of this group of agents has been largely overshadowed by that of other compounds, and few adherents to their cause are still to be found.

Historically, the first truly potent, clinically applicable drug to appear for the treatment of tuberculosis was streptomycin. No attempt at statistical comparative evaluation with other drugs is made at this time. Today, streptomycin is rarely mentioned without its ever-present partner, para-aminosalicylic acid. The delay in the development of organism resistance to streptomycin which this adjunctive agent appears to provide, would seem to have been sufficiently established by a number of comparative studies. Still, I have heard several of my colleagues ask whether or not this is not just a dictum, accepted, handed down and perhaps un-

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true. Personally I have rarely used streptomycin unaccompanied by another drug.

Whether streptomycin or dihydrostreptomycin is to be used often seems of no consequence. Most observers make their choice on the grounds of toxicity, letting the individual case decide whether risk of auditory or vestibular damage is more important. The use of one-half gram of each drug in the delivery of a full gram of active substance has great theoretical advantages but I have seen toxicity to each branch of the eighth nerve thru the use of this combination. The side effects of streptomycin may be reduced by division of the daily dose or by use of twice weekly or thrice weekly schedules. Of great interest, albeit still theoretical in clinical application, has been the demonstration by Berczeller and Berczeller[6] of *in vitro* antagonism between isoniazid and streptomycin and the absence of such antagonism between isoniazid and dihydrostreptomycin. I have seen no clinical evidence of such antagonism but whenever given the choice, I prefer the use of dihydrostreptomycin to streptomycin.

Para aminosalicylic acid is indeed a capricious drug. For many patients it is an evil-tasting, nauseating gastro-intestinal irritant. It may cause a wide variety of toxic reactions, including thyroid hyperplasia, lymphadenitis and allergic reactions. Authors differ widely as to the effective daily dose but a recent study by the Chemotherapy Trials Committee of the British Medical Council[7] would seem to fairly conclusively show that there is no advantage to the use of more than 10 grams per day of the basic active substance. PAS must be well made and must be fresh. Rendering it palatable and less irritating has tested the ingenuity of drug houses. To date the powdered sodium salt has had widest acceptance; the potassium salt seems promising. Combined with probenecid, better blood levels are obtained. Patients, however, object to the huge amounts of material they are required to take. PAS has also been given intravenously. The need for this route of administration is undoubtedly limited.

Oxytetracycline has also been proposed as a satisfactory substitute for PAS as a resistance deterrent.[9, 10] The dosage of 2 to 5 grams per day renders this therapy expensive and the variably reported gastro-intestinal disturbances at the very least would dictate caution in its use. Whether tetracycline hydrochloride will be equally effective and whether the newer combinations of tetracycline hydrochloride with fungicidal agents will eliminate gastro-intestinal irritation awaits demonstration.

To date the most potent anti-tuberculous agent is isoniazid. Its great usefulness stems from its effectiveness at extremely low concentrations, its ability to penetrate all tissues of the body, including tubercle bacillus containing macrophages,[11] and its relative absence of toxicity. In addition, poorly understood anabolic side effects, which continue long beyond the period of resistance development, appear to prevent clinical deterioration.[12, 13] These anabolic effects are produced in far greater degree by iproniazid, the isopropyl derivative of isoniazid, and were it not for concomitant increases in toxicity and reduced antituberculous activity,

iproniazid would probably be the drug of choice. Isoniazid toxicity is expressed most commonly and most seriously in various parts of the nervous system.[1, 2, 3] Peripheral neuritis varies again in frequency in many reports.[14] In my experience, it occurs in about 10 per cent of cases and more frequently at higher dosages. The neuritis can be extremely severe and in some instances appears to be permanent. Pyridoxine is said to be helpful. I have used it, along with glutamic acid, high dosage B-complex vitamins, BAL, Protamide,® chlorpromazine, intravenous procaine and others without convincing effect.

Regarding dosage, the optimum has not been definitely established. In general, children tolerate far higher doses than do adults and old people must be treated cautiously. Our own observations at Sea View Hospital regarding speed of defervescence and rapidity of clinical control suggest that there is distinct advantages to moderate doses (450 mgs. in 3 divided doses per day) over low doses (150 mgs. per day). Three hundred milligrams appears to me to be barely adequate. At 600 mgs., the incidence of toxicity increases.[15] But it is my feeling, statistically unsubstantiated based on but random observations and communications, that doses of 1500 to 2000 mgs. or higher, if feasible, would be distinctly desirable. Biehl, et al[16] state that prior use of pyridoxine prevents peripheral neuritis even at levels of 20 mgs./K of body weight. Also in relation to the higher dosages, attention should be drawn to the work of Middlebrook[17] and Middlebrook and Dressler,[18] who have shown a relationship between catalase negativity and diminished virulency of the tubercle bacillus for the guinea pig when a therapeutic dosage of 8 or more mgs./Kilo of body weight has been administered.

There are few adherents to the use of isoniazid alone.[19, 20, 21] However, the curious capacity of this drug to sustain life and well being virtually indefinitely, even in the face of unconverted sputum, allows full exploitation of the problem of uncombined therapy. At our own institution, our Director of Pediatrics, Dr. Bret Ratner,[22] has successfully treated tuberculous meningitis in children through the use of isoniazid alone.

In general, however, most observers prefer to combine isoniazid with PAS or with streptomycin or with both. No convincing superiority of any of these three regimens has been unequivocally demonstrated although the Chemotherapy Trials Committee of the British Medical Council[7] has recently noted that at three months, the use of isoniazid plus daily streptomycin has given the highest percentage of x-ray improvement and the lowest incidence of organism resistance to isoniazid. On genetic grounds, the combined use of all three drugs has theoretical superiority over any two.

Another drug of interest but of problematical position in the antimicrobial armamentarium is pyrazinamide. This drug has noteworthy short-term effectiveness but rapidly elicits resistance. Current interest centers about its combined use with isoniazid. Satisfactory therapeutic results have been reported by McDermott and his associates[23, 24] and by Moyer and Schwartz.[25, 26] They have not been overly alarmed by the toxicity observed.

Other studies, on the other hand, and notably that of Potter,[27] indicate an incidence of hepatotoxicity that seriously prejudices utilization of this drug as a first-choice agent.

Viomycin is another drug with undoubted but limited activity against the tubercle bacillus. The recommended dosage is 2 grams, twice weekly and at this dosage, toxicity is infrequent. Nephrotoxicity is the most serious problem. The place of this drug has been fairly well established since its lesser effectiveness and relative toxicity reduces it to a level of secondary importance. There appears to be general agreement that its greatest value is as an adjunct to surgery when there is organism resistance to the first line drugs. In this respect its adjunctive status resembles the current status of pyrazinamide.

Several attempts have been made to find a salt of isoniazid which will allow the higher doses which are theoretically desirable. In each instance to date, the attainable increased dosages appear to have been accompanied by a concomitant diminished relative efficacy. This is apparently true of D-glucuronolactone isonicotinyl hydrazone and others, so that no appreciable advantage over isoniazid is discernible. A sulphonic acid derivative is currently under investigation and is said to provide a wide range of safety. The many questions as to the effectiveness and resistance remain unanswered to date.

Available today are chemical combinations of streptomycin and isoniazid, and PAS or AS and isoniazid.[28] To my mind the former offers no advantage; the latter are still experimental.

Cycloserine,® first studied and reported upon in February 1955 by Epstein, et al[29, 30] gives large promise in a particularly difficult type of case, the retreatment case. Dosages of one to one and a half grams per day for six weeks to four months produced sputum conversion in 30 of 37 cases. X-ray improvement was seen in 28. Questions regarding sustained effect, combined therapy, resistance, long term toxicity and so on remain unresolved. It is our hope that before the current meeting is over, Dr. Epstein will have answered for us many of the remaining questions. Of some interest is the fact that acute toxicity is manifested by convulsions. This effect on the central nervous system is similar to that often seen with iproniazid and occasionally with isoniazid, particularly in people with convulsive tendencies. Cycloserine® is an antibiotic, extracted from the streptomyces orchidaceous. It is effective against a number of organisms as well as the tubercle bacillus, especially in those commonly infecting the genito-urinary tract. It has startlingly little *in vitro* activity and relatively little in animals. Nonetheless, its effectiveness in humans seems undeniable.

Having thus roughly appraised the drugs at our disposal, we may turn to that other variable, the patient, to see if we can employ the agent or combination of agents most likely to succeed. In doing this, we must utilize our total body of observations, often seemingly unrelated, and from them gradually evolve our philosophy of therapy. The reasons for this seeming indirection are many and are based upon the extreme difficulties encountered in the interpretation of therapeutic results. First and fore-

most among the difficulties is the totally unpredictable course of untreated tuberculous disease in any individual. We have all seen the disobedient and unheedful patient who has spontaneously closed his cavities and controlled his disease; similarly we have all seen the patient who has obeyed the letter of the law, yet has met nothing but frustration.

The second factor which has made interpretation of results difficult has been the virtual impossibility of any two clinicians to agree as to the classification of any given disease. Exudate to one, is caseation to another. Cavities become cysts. And highlights may be cavitation, bronchiectasis or emphysema within fibrosis. Now that chemotherapy with its suppressive effect is so universally available, the sputum, once a reliable indicator of cavitation, has become more misleading than helpful. Our misery is further compounded by our own classifications wherein the term "far-advanced" with its implication of a serious state, may indeed be applied to a benign, resolving lesion, of far less significance with regard to prognosis than a caseous-pneumonic of limited extent. Thus our interpretations and classifications mislead us and make it difficult for us to communicate in like tongue.

In spite of this growing confusion, one fact has become increasingly obvious as our chemotherapeutic studies progress. This fact is that the fresh case, almost irrespective of extent of disease, but detected early, will respond to treatment in an entirely more satisfactory manner than will that with the chronic fibro-caseous lesion. This applies specifically to the "retreatment case" but it seems to me that the limiting factor is not the prior use of the same or another antimicrobial, but the *time* that has elapsed and the manifest opportunity for development of inelastic, irreversible fibrosis. The chronic, thick-walled cavity, the wall of which has been the site of much fibroblastic activity and which contains heavy bands of collagen fibers, some hyalinized, cannot close as readily as that which is seated within elastic, still-yielding lung tissue which has a wall composed of vascular granulation tissue, a variable amount of unorganized caseation and an outer layer of non-specific perifocal inflammatory exudate. Similarly with the specific exudate. It may be expected to reabsorb and disappear from the x-ray more rapidly than will the partially organized, partially entrapped, more profoundly destroyed infiltrates with their impaired drainage.

Thus, duration of lesion has become a factor of high significance. Arriving at estimates may be difficult, since it has now become a commonplace experience with all phthisiologists to have seen the disappearance under chemotherapy of a nodular lesion long present and always considered "productive." Its disappearance implies its essentially exudative and therefore reversible character. In general, nodular lesions, unless quite dense, should be considered with special care.

The second factor to be considered in instituting proper therapy in any given case is that relating to organism resistance to the proposed antimicrobial. In some instances, this will far surpass in significance the question of the lesion's duration. Where resistance does not exist, it has no significance with respect to choice of drug. True total primary re-

sistance is variously reported but must be rare; the presence of a few resistant organisms in the sputum is normal and anticipated. When primary resistance does occur the suspicion of inoculation from a treated case is to be considered. In any event, we do not delay institution of therapy until our resistance studies are complete. In choosing the proper drug, it is imperative to remember that resistance to *one* of a proposed combination of two drugs, is tantamount to therapy with the single drug to which there is no resistance. It will behave in the manner of a single drug and resistance will develop to it in the same way as to any unpaired drug.

The third factor which should influence the decision regarding choice of antimicrobial agent is that based on an early total evaluation of the case and an estimate of what total benefits may be anticipated. Thus one perforce must consider the patient's age, physical state, social outlook, past history, behavior pattern and pulmonary function. The chronic "sign-out" may require primary irreversible, definitive therapy. The need for prompt rehabilitation may be paramount. A given patient may not be psychologically suited to long-term therapy. Similarly, if ultimate surgery is anticipated, it is a mistake to delay it beyond a cooling-off period, beyond the period of drug sensitivity, beyond the patient's patience. I am convinced that waiting for sputum negativity before operating is an error, that the risk of earlier surgery is not appreciably greater, that when true sputum negativity is achieved, the indications *for* surgery are reduced, not increased.

It is usually possible to lay out a total program for any given patient at time of admission. Barring change, this should be followed, but systematic subsequent re-evaluations should be made. If it is obvious that no therapy will cure the patient, he should still be treated if only for the physical and psychological comfort such therapy provides. If on early evaluation surgery seems obvious and inevitable, preparations should be made with that in mind. If it seems probable that medical therapy will suffice, the drugs should be chosen and treatment instituted, but not before sputum cultures for sensitivity determinations have been begun since any additional available data may later be helpful. Adjunctive therapy should not be feared. There is no sound basis for the wave of abandonment of medical collapse measures. Pneumothorax and pneumoperitoneum, but especially the former, are indeed useful procedures in carefully selected and handled cases. And they are especially useful during the period of early chemotherapy before resistance has developed. When surgery cannot be considered for one reason or another, and where medical therapy alone cannot be expected to evoke definitive cure, it is not proper to abandon the patient without giving careful consideration to pneumothorax or pneumoperitoneum. Under cover of sound antimicrobial therapy, the former fears of empyema, bronchopleural fistula, unexpandable lung, late reactivations, etc. are rendered virtually without foundation.

With regard to the specific drugs, the decision again rests with the early total evaluation. Thus in dealing with a minimal, exudative lesion, wherein one may anticipate complete success with something approaching

total eradication, it is my philosophy to use isoniazid, streptomycin and PAS. It is my aim in this instance to eliminate the disease and I doubt if the organism will be unfettered long enough to develop resistance. Realizing that we are holding little in reserve, I still believe we are allowed the luxury of a gamble in these instances. The dose would be daily streptomycin for one month at least, 450 to 600 mgs. of isoniazid and 12 grams of PAS.

Conversely, given a far-advanced, cavitary and fibrotic disease wherein the preliminary estimates clearly predict a prolonged course of antimicrobials, it is my philosophy to provide that patient with some chemotherapeutic agent to which his organisms are sensitive for *as long a period of time as possible*. I would therefore institute therapy with isoniazid and PAS alone unless toxic reactions ruled otherwise and would continue such therapy as long as possible. The duration would depend upon the sensitivity studies. With evidence of resistance development, I would immediately add streptomycin to the other two drugs. With development of resistance to PAS before isoniazid (an unusual phenomenon) I should substitute streptomycin for the PAS since we know that streptomycin and isoniazid offer each other some mutual protection. Upon development of resistance to either of these two, I should institute therapy with oxytetracycline. If it were the streptomycin which developed resistance, I should discontinue it; if the isoniazid, I should continue it. My aim would invariably be the provision of protracted therapy with an effectual drug.

In any event, I would never discontinue isoniazid regardless of the substitutions made unless toxicity or sensitivity forced discontinuance. Whether the anabolic effects are responsible is not clear but with or without resistance, in my experience, patients under isoniazid therapy spread less frequently. Furthermore, I have yet to encounter a report of meningitis occurring during therapy. This is not true of streptomycin during courses of which I have seen fatal miliarys and meningitides develop.

The phrase "buying time" has been used. I think it is a good one and highly descriptive. With proper chemotherapy, we are attempting to hold destructive forces in check until the body can effect annihilation or encirclement and healing. Thus adequate chemotherapy invariably introduces the time factor.

As to dosage, the normal 12 grams per day of PAS, 450 mgs. of isoniazid in the average sized patient and bi-weekly streptomycin are considered standard. If the disease is acute, streptomycin should be given thrice weekly or even daily for one or more months. It has been suggested that pyridoxine be given immediately in divided doses of 150 to 300 mgs. per day to avoid isoniazid neuritis. It is said that if you wait for symptoms, pyridoxine is less effectual.[16] This work is not yet on firm ground and I do not routinely use it. If neuritis develops, I prefer to discontinue isoniazid and resume at a later date at a lower dose.

For the present, I believe that pyrazinamide alone or in combination should be considered experimental. It is not yet ready for routine use as

a primary drug; its field of usefulness begins when isoniazid and streptomycin are through and in this respect, it resembles viomycin. Again I emphasize that should either of these be added to the regimen, isoniazid should not be discontinued.

Cycloserine® is indeed experimental and similarly cannot be recommended until a great deal more work has been completed.

Regarding the duration of therapy, investigators vary in their estimates. My own experience has been rather clear-cut. Short term therapy — three months to six months — has often been followed by relapse. Longer term therapy — six months to one year — has much less frequently been followed by relapse. After one to one and a half years of therapy, relapses have been rare. I believe that one year of therapy should be considered minimum, one and a half years desirable. The statistical advantage of more than one and a half years' therapy has not been calculated because of the paucity of relapses in the one to one and a half year regimens.

Certain exceptions to this schedule are, I believe, valid. In the post-surgery patients without tuberculous residua, six months of therapy post-operatively has been satisfactory. Similarly, in the recently acquired primary, where it can be established that tuberculin conversion has been of no more than a few months' duration, I feel that three to six months' therapy should suffice. I treat these with isoniazid alone. Many years will elapse before the wisdom of this course will have been proved. However, justification is given by the relative absence of toxicity of isoniazid and by the fact that in the experimental animal the only reconversions to negative occurred where therapy was instituted promptly after infection.

Pleural effusions presumed to be tuberculous should have the status of the minimal tuberculous infiltrate and should be treated as such. This means a minimum of one year of therapy. Since organisms are rarely recovered for sensitivity studies, I arbitrarily use isoniazid and PAS, not hesitating to discontinue the PAS if it is not well tolerated. The great advantage of isoniazid here is the ready penetration of pleural fluid by this drug.

A word must be said about tuberculous empyema with broncho-pleural fistula. Until the introduction of isoniazid, this condition, often a complication of ill-advised pneumothorax, was considered an acute surgical emergency because of its frequent and sudden induction of severe contralateral disseminations. This fortunately is now rare. When it does occur, we are given time for reflection. In many instances medical therapy alone suffices to allow fistula closure and fluid re-absorption. In several instances I have seen chronic fistulae which persisted benignly for years.

Miliary tuberculosis remains a serious condition since its source is an extra-pulmonary focus and its route of dissemination is the blood stream. A third or more are ordinarily associated with meningitis since the source is often a caseous cerebral focus adjacent to the sub-arachnoid space. In other instances the same hematogenous dissemination may seed the meninges as well as the lungs. Streptomycin or streptomycin and PAS have been distressingly unsuccessful in preventing this complication but

it is in this field that isoniazid exhibits its most spectacular usefulness. Miliary tuberculosis calls for one to one and a half years' therapy with isoniazid and PAS. In acute cases I add streptomycin daily for one to three months followed by twice weekly injections thereafter.

For meningitis isoniazid has been used alone but most clinicians prefer combination with streptomycin and PAS. The former should be given in high dosage — 8 to 10 mgs. per kilo — until significant spinal fluid changes are noted. The streptomycin should be given at a level of one gram per day for at least one month in the acute case and may then be reduced to twice weekly. Intrathecal therapy is neither necessary nor desirable unless the organism is isoniazid resistant and streptomycin sensitive in which case consideration may be given to intrathecal streptomycin therapy. Results in meningitis regimens which include isoniazid have been highly felicitous.[20, 21]

Finally a word must be said about ambulatory therapy. This must be differentiated from "home care" which, under proper conditions, is entirely feasible. Opinions are divided[32] as to the possibility of successfully treating patients under full ambulation. Based upon my own clinical observations in representative numbers of such cases, I would summarize by saying that:—

1. For early, exudative non-cavitary lesions, modified bed rest for one to three months is desirable but not essential.
2. For early, exudative small-cavity cases, the percentage of cavity closures is materially increased by modified bed rest of three months' duration.
3. For caseous-pneumonic or fibro-caseous larger cavitary lesions, three to six months' modified bed rest is usually essential unless supplemented by successful pneumothorax or pneumoperitoneum in which case one to three months may suffice.
4. Old, predominantly fibrotic non-cavitary lesions do not appear to benefit greatly from bed rest.
5. Pleural effusions, presumed tuberculous, should be treated as minimal exudatives.
6. Primaries require no bed rest unless unusually extensive.
7. Miliaries require strict bed rest for at least three months.

SUMMARY

1. Tuberculosis therapy has been complicated rather than simplified by the introduction of newer effective drugs.
2. Omitting the sulphones (for which there has been some recent renewal of interest) and the semicarbazones, the important drugs are isoniazid, streptomycin and PAS in various combinations.
3. Potentially important are pyrazinamide and oxytetracycline.
4. Less effectual against the tubercle bacillus but with special fields of usefulness are iproniazid and viomycin.
5. Of uncertain usefulness are salts of isoniazid and chemical conjugations between streptomycin and isoniazid and PAS or AS and isoniazid.
6. Still under investigation but immensely interesting is Cycloserine.®

7. Choice of drug regimens depends upon initial evaluation of the patient, estimation of sensitivities and minute knowledge of the history of the disease in the given patient.

8. Drug regimens should always include isoniazid unless allergy or toxicity rule otherwise.

9. Minimal lesions call for concurrent therapy.

10. Protracted disease calls for consecutive therapy.

11. Therapy should be continued for one to one and a half years excepting in special instances, such as the post-surgery patient or the recent primary when duration of therapy may be considerably less.

12. Pleural effusions, presumed tuberculous, call for isoniazid or isoniazid plus PAS therapy.

13. Miliary tuberculosis requires combined therapy, one of the members of which must always be isoniazid.

14. Ambulatory therapy is feasible in many instances but is allowable only after careful analysis of the case.

RESUMEN

1. Con la introducción de las nuevas drogas, el tratamiento de la tuberculosis se ha hecho más complejo en lugar de simplificarse.

2. Exceptuando las sulfonas (por las que se ha renovado recientemente el interés) así como las semicarbazonas, las drogas importantes son la isoniacida, la estreptomicina y el PAS, en sus diversas combinaciones.

3. Son potencialmente importantes la pirazinamida y la oxitetracilina.

4. Menos efectivas contra la tuberculosis pero con ciertos campos para su aplicación son la iproniacida y la viomicina.

5. Son de cierta utilidad las sales de isoniacida y los compuestos químicos de estreptomicina e isoniacida y de PAS o AS e isoniacida.

6. La Cicloserina está aún bajo investigación si bien es inmensamente interesante.

7. La elección del régimen de drogas depende de la estimación inicial de la enfermedad en el sujeto, su sensibilidad y el minucioso conocimiento de la historia en cada caso.

8. Los regímenes de drogas deben incluir siempre la isoniacida a menos que la alergia o la toxicidad lo impidan.

9. Las lesiones mínimas requieren terapia combinada.

10. La enfermedad prolongada necesita tratamiento a largo plazo.

11. El tratamiento debe continuarse durante uno a uno y medio años con excepción de ciertos casos, tales como el enfermo recien operado y la infección primaria reciente pues entonces el tratamiento debe ser más corto.

12. Los derrames pleurales que se supone sean tuberculosos requiere el uso de isoniacida sola o asociada al PAS.

13. La tuberculosis miliar requiere terapia combinada uno de cuyos componentes debe ser siempre la isoniacida.

14. La terapia ambulatoria es practicable en muchos casos, pero es permisible sólo después de un análisis cuidadoso del caso.

RESUME

1. Le traitement de la tuberculose a été compliqué pultôt que simplifié par l'apparition des nouveaux produits efficaces.

2. Laissant de côté les sulfones (pour l'intérêt desquels il y a une renaissance récente) et les sémicarbazones, les produits importants son l'isoniazide, la streptomycine et le P.A.S. en combinaisons variées.

3. La pyrazinamide et l'oxytétracycline sont des produits de grande efficacité.

4. L'iproniazide et la viomycine sont moins efficaces contre le bacille tuberculeux, mais ont des cadres particuliers d'activité.

5. Les sels d'isoniazide et les combinaisons chimiques entre streptomycine et isoniazide et P.A.S. ou AS et isoniazide sont d'une efficacité incertaine.

6. La Cyclosérine® est encore au stade de l'expérimentation mais elle est intéressante.

7. Le choix de la conduite thérapeutique dépend de l'état initial du malade, de l'évaluation de sa sensibilité aux produits, et de la connaissance précise de l'histoire de sa maladie.

8. Les traitements médicamenteux devraient toujours comprendre l'isoniazide, à moins que le malade ne puisse supporter ce produit.

9. Les lésions minimes demandent un traitement combiné.

10. L'atteine étendue nécessite une thérapeutique ininterrompue.

11. Le traitement devrait être continué pendant un an à un an et demi, sauf dans des cas exceptionnels, tels que pour les malades qui ont été opérés ou les primo-infections récentes, pour lesquels la durée du traitement peut être bien moindre.

12. Les épanchements pleuraux présumés tuberculeux nécessitent un traitement par l'isoniazide, ou par l'isoniazide combiné au P.A.S.

13. La tuberculose miliaire nécessite un traitement combiné dont l'un des produits doit toujours être l'isoniazide.

14. Le traitement ambulatoire est applicable dans beaucoup de cas, mais seulement après analyse minutieuse du cas.

ZUSAMMENFASSUNG

1. Die Behandlung der Tuberkulose ist durch die Einführung neuer wirksamer Medikamente eher komplizierter als einfacher geworden.

2. Lasst man die Sulfone (für die in neuerer Zeit wieder ein gewisses Interesse erwacht ist) und die Semikarbazone unberücksichtigt, so sind die wichtigen Medikamente Isoniazid, Streptomycin und PAS in verschiedenen Kombinationen.

3. Dem Pyrazinamid und Oxytetracyclin kommt möglicherweise auch eine Bedeutung für die Behandlung der Tuberkulose zu.

4. Weniger wirksam gegen das Tuberkelbakterium sind Iproniazid und Viomycin, die aber trotzdem für bestimmte Gebiete ihren Nutzen haben.

5. Von ungewissem Nutzen sind Salze des Isoniazid und chemische Verbindungen zwischen Streptomycin und Isoniazid sowie PAS oder AS und Isoniazid.

6. Noch in Erprobung, aber ausserordentlich interessant ist Cycloserine®.

7. Die Auswahl der Medikamente hängt ab von dem Befund des Patienten, von der Resistenzbestimmung und von der genauen Kenntnis des Krankheitsablaufes des Patienten.

8. Jede Kombinationstherapie sollte Isoniazid einschliessen, wenn nicht allergische oder toxische Erscheinungen dieses verbieten.

9. Geringfügige Veränderungen erfordern eine gleichzeitige Therapie.

10. Fortgeschrittene Erkrankungen erforden eine aufeinanderfolgende Therapie.

11. Die Behandlung sollte sich über 1 - 1½ Jahre erstrecken mit Ausnahme besonderer Fälle, wie postoperativer Befunde oder frischer Infektionen, wo die Behandlungsdauer wesentlich geringer sein kann.

12. Pleuritis exsudativa sollte mit Isoniazid oder Isoniazid und PAS behandelt werden.

13. Die Miliartuberkulose erfordert Kombinationsbehandlung, bei der stets das Isoniazid beteiligt sein muss.

14. Ambulante Behandlung ist in vielen Fällen möglich, sollte aber nur nach sorgfältiger Prüfung des Falles erlaubt werden.

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P-Pulmonale in the Precordial Leads and A Review of the Mutability of the P-Waves in Chronic Cor Pulmonale

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Introduction

While peaked and tall P-Waves in leads two and three are often seen with cor pulmonale, one encounters only occasionally such a formation in lead AVF and rarely in the precordial leads over the right side of the heart. The present study reports the occurrence of a peaked P-Wave of high voltage in leads V-2 and V-3 obtained from two patients with severe chronic cor pulmonale. In addition to that observation, this investigation is devoted to the multiplicity of changes in contour, voltage and direction of the P-Wave in cor pulmonale during protracted electrocardiographic follow-up. An evaluation of such serial changes can be misleading without simultaneous clinical appraisal of the individual. In some patients the peaked and tall P-Wave may lose its characteristics, it may become inverted, then peaking and high voltage may reappear, and the same patient may on and off yield electrocardiograms without the typical pattern of cor pulmonale. Thus temporarily there will be seen merely right axis deviation but not any more the previously diphasic T-2 nor inverted T-3, and the tapering as well as the high amplitude of P-2 and P-3 will have receded. This transient normalcy of the electrocardiogram must not be used as a criterion for the patient's cardiac normalcy. That consideration is especially important when major surgery is contemplated.

One must bear in mind that peaked P-Waves occur without cor pulmonale due to various factors, such as tachycardia, postural cardiac changes, hyperthyroidism and congenital heart disease with atrial enlargement. It must also be remembered that with right atrial enlargement as seen in cor pulmonale (secondary to lung conditions) the P-Wave will tend to have a pointed summit and high voltage while with left atrial enlargement the P-Wave is usually broad, of low voltage and notched. However, the configuration of the abnormal P-Wave is not always diagnostically conclusive. A tall peaked P-Wave can be encountered with mitral stenosis due to rheumatic heart disease.[1] Lowering of blood potassium may increase the height of P-2 and P-3.[2]

Of special interest are the cases of chronic cor pulmonale without showing at any time a tall or peaked P-Wave. One may see on the electrocardiogram marked right axis deviation, a miniature P-1, extremely shallow T-2 and T-3, small Q-Waves in L-2 and L-3, and P-2 and P-3 will be

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conspicuous due to their normal voltage in contrast to the extremely low voltage of the T-Wave in the same lead. Not infrequently I have seen this phenomenon supported by autopsy findings.

This paper is confined to three case reports: 1. Chronic cor pulmonale secondary to pulmonary artery thrombosis; 2. Chronic cor pulmonale in a patient with pulmonary tuberculosis; 3. Chronic cor pulmonale secondary to asthma and irreversible pulmonary emphysema.

Two patients had episodes of arrhythmia. Inasmuch as they were on digitalis therapy, a drug effect was suspected.

Case 1: A 36 year old white man was admitted on January 23, 1952 to the Veterans Administration Hospital, Bronx, New York, with the chief complaint of shortness of breath and the need of three pillows at night during the past half year. He was in good health until one year prior to hospitalization when, after walking 10 blocks, he suddenly experienced difficulties in breathing and fainted. There was loss of consciousness for five or perhaps 10 minutes. On resuming the walk he noted marked shortness of breath. There was no chest pain or evidence of convulsions. Following the collapse, long or rapid walking would be associated with a sensation of lack of air and a bluish discoloration of the face. Six months before admission he became aware of dyspnea on even slight exertion. Cyanosis had become constant by now, remained even without exertion but increased during physical effort. There was no history of cough, hemoptysis, fever, ankle edema, or nocturia. Occasionally there appeared palpitation with the dyspnea. Several months prior to admission a roentgenogram at the local Health Center was reported as showing some pulmonary infiltrate.

Physical Examination: Height 180 cm. Weight: 146 lbs. Blood pressure 104/74. Cyanosis of the lips and nailbeds. Marked cyanosis of the entire face while in the supine position. Distended neck veins which display pulsations and filling from below in the supine position. Orthopnea. Chest of good expansion, lungs normal on percussion and auscultation. Examination of the heart revealed a point of maximum impulse in the sixth ICS, just outside the midclavicular line. The heart sounds were of good quality and P-2 was greater than A-2. There was a harsh long medium pitched systolic murmur heard best in the fourth ICS to the left of the sternum and transmitted towards the apex and pulmonic area. There was a questionable thrill when in the knee elbow position. There was no diastolic murmur and there was NSR with a rate of 92. There was no systolic retraction of the precordium or paradoxical pulse. No gallop or friction rub. The abdomen was slightly protuberant and held tensely but there was no fluid wave or shifting dullness. The abdomen was difficult to palpate and the liver edge could not definitely be felt but there was the impression of a mass and dullness three finger breadths below the RCM. There was no other mass or tenderness to palpation. There was slight clubbing and cyanosis of all fingers and toes.

Laboratory and X-ray findings: Hgb. 14.1 gm. RBC 4,150,000. WBC 9,200 with 64 polys, 1 L, 3 M, and 2 E. Hematocrit 39 per cent. Sedimentation rate 12 mm. per hr. Urinalysis normal. Serum chlorides 100. CO_2 50 volume per cent. BUN 19. Sodium 133. Potassium 4.3. Serology negative. Six blood cultures negative. Serum bilirubin 0.8. Thymol turbidity 3.6. Van Den Bergh direct 0.4, indirect 0.4. Cephalin flocculation 1 plus. Alkaline phosphatase 13.3. Total proteins 6.3 with albumin 4.1, globulin 2.2. One culture of gastric washings for acid fast bacilli on February 5, 1952 was positive. An EKG on admission revealed changes compatible with right ventricular hypertrophy and strain and atrial hypertrophy. X-ray film of the chest revealed a fibronodular and somewhat soft infiltrate in the upper third of the right lung field and some scattered infiltrate in the apex of the left lung field. Cardiovascular shadow showed some enlargement in the transverse diameter and some prominence of the hilar vascular shadow. Angiocardiograms showed marked dilatation of the left main pulmonary artery suggestive of pulmonary hypertension. The pulmonary vasculature in the right lung field appeared relatively normal. In the lower two thirds of the left lung field there was a marked diminution of the pulmonary vasculature with absence of visualization of the main stem pulmonary arteries to this area. Cardiac catheterization revealed marked pulmonary hypertension.

Following clinical improvement the patient left the hospital against medical advice on May 7, 1952. Admitted to Veterans Administration Hospital, Castle Point, New York on September 19, 1952. On admission he appeared acutely ill with extreme dyspnea, orthopnea, edema of right arm and ankles and cyanosis. There was pulsation of neck vein, filling from below. Heart rate 120. Ascites. Liver five finger breadths below costal margin. The roentgenogram showed cardiac enlargement in all diameters. On oblique views the right ventricular bulge was markedly accentuated. There was no

evidence of left atrial enlargement on esophograms.

Venous pressure was 200 H20 on March 18, 1953. Circulation time, performed with decholin, was 24 secs.

He expired on May 16, 1953.

Extract from Necropsy Findings on Full Autopsy

1. Primary pulmonary atherosclerosis and thrombosis, bilateral, involving small, medium and large vessels.
2. Cor pulmonale. Heart weighed 550 gms. The wall of the right atrium was hypertrophied and 3 to 5 mm. thick.
3. Cardiac cirrhosis of the liver.
4. Chronic pulmonary tuberculosis.
5. Pulmonary emphysema, left upper, left lower, and right upper lobes.
6. Emphysematous cysts, right upper lobe.

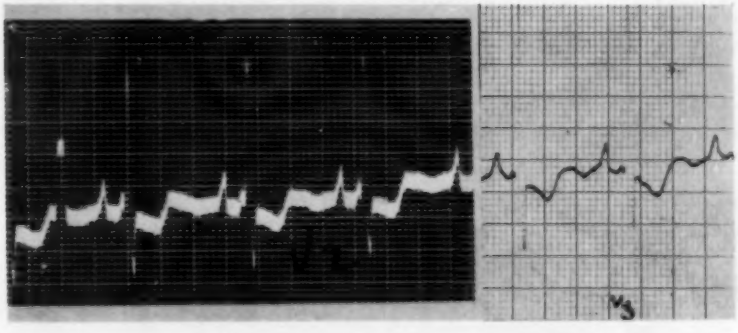
ECG. changes. January 24, 1952. No medication given. Regular sinus rhythm, rate 99. Right axis deviation. PR 0.14. QRS 0.09. QT 0.32. P-1 0.15 mv. P-2 peaked, with ascending limb 0.3 mv. and descending limb 4.0 mv. P in AVL inverted. P in AVF peaked, 0.3 mv. T-1 upright. Tendency to diphasic T-2. T-3 inverted, also T in AVF. Shallow T in AVR and less deep than P wave in same lead. T inverted in V-1 and upright from V-2 to V-6. ST depressed in L-2, V-2, V-3 and V-4. Small Q in L-3 and AVF. Prominent R in AVR and V-1. In V-4 to V-6 the depth of the S-waves causes a reversal of the RS ratio. In V-2 the P-wave is peaked and of 0.3 mv.

Interpretation: Cor pulmonale. April 18, 1952. P-2 0.2 mv. P. in V-2 rose to 0.4 mv.; and P in V-3 is of 0.25 mv. April 16, 1953. As in previous ECGs, the inverted QRS in L-1, the tall R in L-3 and AVF indicates R.A.D. Tall upright R in V-4 and CF-4 points to an added left electrical axis deviation factor. No reversal of the RS ratio as seen January 24, 1952. Rate 90. PR 0.16. QRS 0.10. T-1 upright. T-2 diphasic and miniature. T-3 inverted. T inverted in V-2. P-2 of 0.2 mv. P is peaked in V-3 and of 0.4 mv. P became upright in CF-4. ST depressed in L-2, V-3, V-4 and CF-4. In V-3, V-4 and CF-4 ST merges with miniature diphasic T-waves.

Interpretation: The combined right and left electrical axis deviation indicated either postural cardiac factors or enlargement of the heart to the right as well as to the left. This ECG is probably expressive of the coexistence of both conditions.

Comment: The autopsy evidence permits the deduction that in this case the peaked P waves were due to cor pulmonale. During the course of illness P-2, when highest, was 0.3 mv. and almost isoelectric when lowest. P in V-2 and V-3 were 0.4 mv. when highest. This tall peaked precordial P-wave apparently becomes manifest only if the right atrial enlargement reaches a marked degree.

Case 2: A white man, 40 years of age. Onset of pulmonary tuberculosis in 1945. He had right thoracoplasty with removal of seven ribs completed March 9, 1948. Right upper lobectomy was performed November 30, 1948. Cor pulmonale was diagnosed in 1952. He since had recurrent episodes of cardiac decompensation. The sputum was still positive for tubercle bacilli.



V-2 V-3

FIGURE 1: P-pulmonale in precordial leads over the right side of the heart. Severe cor pulmonale due to pulmonary artery thrombosis. On April 18, 1952 peaked tall P-wave in V-2. On April 16, 1953 peaked tall P-wave in V-3.

ECG. findings. On June 28, 1954, P-2 reached 0.5 millivolts. P in V-2 rose to 0.3 mvs. as compared with 0.2 mvs. on May 24, 1954. On July 15, 1954, P in V-3 also rose to 0.3 mvs.

This case demonstrates that in severe cor pulmonale there may develop, in addition to a high peaked P-wave in lead two, also a P-pulmonale in the precordial leads over the right heart.

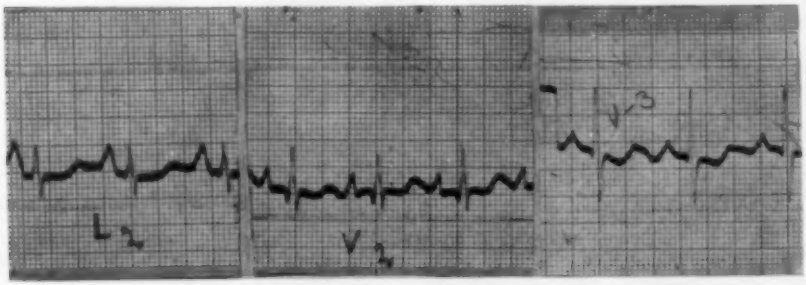


FIGURE 2: P in L-2 0.5 mv. P in V-2 and V-3 0.3 mv. Prominent P-waves in precordial leads over right heart due to severe cor pulmonale resulting from pulmonary tuberculosis.

Case 3: A white male veteran who at the age of 34 years developed in September 1944 bronchial asthma, probably of allergic etiology and permanent pulmonary emphysema ensued. Since 1949 to December 1953, he represents a respiratory cripple who is dependent on the administration of oxygen even when not being in status asthmaticus. Cor pulmonale was diagnosed in 1949 on the basis of the electrocardiogram. The roentgenogram did not show enlargement of the heart, however the width of the right pulmonary artery measured 14 mm. suggesting the maximal normal width. Digitalis was needed frequently during the protracted period of hospitalization whenever episodes of right cardiac failure occurred.

Serial ECG. changes. December 29, 1949. P-2 and P-3 0.3 mv. September 20, 1951. P-2 and P-3 inverted. October 18, 1951. P-2 and P-3 upright, and 0.2 mv.

Interpretation of numerous serial observations: The low voltage of QRS-1, the relatively high upright R in AVF and the S-waves in left precordial leads point to right axis deviation as seen in pulmonary emphysema. This is here a sustained pattern. The transient P-wave abnormalities observed in connection with severe asthmatic attacks may be expressive of temporary enlargement of the right atrium. One may assume the existence of cor pulmonale in terms of a concentric hypertrophy of the right ventricle which does not need to be recognizable on the x-ray film. Return of the P-waves to a normal pattern indicates that the decrease of the circulatory load on the right heart is

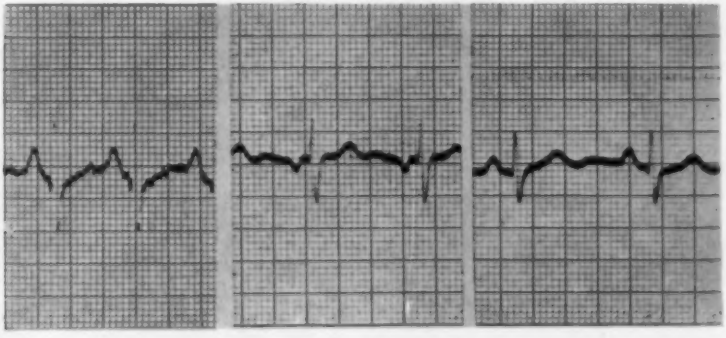


FIGURE 3: Mutability of the P-wave in chronic cor pulmonale secondary to pulmonary emphysema. Peaked tall P-wave in lead two on December 29, 1949. Inverted P-wave in lead two on September 20, 1951. Normal P-wave in lead two on November 18, 1953.

reflected in the improved ECG. The flattening out of T-2 and T-3 during respiratory stress, together with the concomitant P-wave abnormalities, is in line with severe right ventricular strain as seen in cor pulmonale. When the P and T waves become abnormal and ST depression becomes apparent with it, then an element of coronary insufficiency is to be considered, too. However, the effect of electrolyte inbalance and a status approaching asphyxiation may also be reflected in such an ECG.

June 22, 1953. P-2 peaked, ascending limb 0.4 mv. and descending limb 0.5 mv. November 18, 1953. Right axis deviation. Normal complexes.

Comment: A review of serial electrocardiographic changes embracing four years permits the conclusion that in chronic cor pulmonale due to pulmonary emphysema, the P-wave in leads two and three may undergo a transformation from the tall peaked contour to inversion. At times the entire pattern of cor pulmonale may give place to normal complexes, without losing the right axis deviation. Nevertheless, concomitant clinical observation shows that even during the absence of a pathological electrocardiographic pattern pulmonary emphysema may necessitate the continuation of nasal oxygen administration.

Temporary loss of the characteristic contour of the P-pulmonale and episodes of electrocardiographic remissions of the cor pulmonale pattern toward normal complexes do not necessarily signify anatomical cardiac normalcy. Such electrocardiographic improvements may frequently accompany the clinical improvement of cardio-pulmonary insufficiency during long standing cor pulmonale before the fatal cardiac decompensation ensues.

Acknowledgement: The files from the Veterans Administration Hospital, Bronx, N. Y., were utilized for presentation of data on the first case. I am greatly indebted to Dr. Bernard Barshay, Pathologist at Castle Point, whose autopsy findings were included in that case report. The electrocardiograms obtained at Castle Point were taken by Mr. Francis Brangwin, Technician. For photographing the ECG tracings in preparation for publication, I am indebted to Allen Webb, Ph.D.

Addendum: Autopsy performed on Case No. 2 in November, 1954 showed marked cor pulmonale with conspicuous enlargement of the right atrium.

SUMMARY AND CONCLUSIONS

In marked right atrial enlargement due to thrombosis of the pulmonary arteries there were observed not only peaked P-Waves in leads two and three but also in the precordial leads V-2 and V-3 where the amplitude reached 0.4 millivolts.

In severe cor pulmonale resulting from pulmonary tuberculosis there were noticed, in addition to a high peaked P-Wave in lead two, serial changes in leads V-2 and V-3 with an increase in the P-Waves to 0.3 millivolts in these two leads.

In the absence of other causes the tall peaked P-Wave in the precordial leads over the right side of the heart may serve as a confirmatory sign of severe cor pulmonale.

The variability in shape, size and direction of the P-pulmonale during protracted illness is demonstrated in a more common case, namely chronic cor pulmonale due to pulmonary emphysema.

RESUMEN Y CONCLUSIONES

En el marcado crecimiento atrial debido a trombosis de las arterias pulmonares se observaron no sólo angulación de las ondas P en dos y tres, pero también en las precordiales V2 y V3 cuando la amplitud llegó a 0.4 milivots.

En el cor pulmonale severo resultante de tuberculosis se notaron además de una onda alta angulada P end os, cambios en la serie en V2 y V3 con un aumento de lasondas P a 0.3 en estos dos puntos.

En ausencia de otras causas la onda P elevada en las precordiales durante enfermedad prolongada, se demuestra en un caso más común o sea en el cor pulmonale debido al enfisema pulmonar.

RESUME

Dans l'hypertrophie de l'oreillette droite, due à la thrombose des artères pulmonaires, on observa des ondes P en pic, non seulement dans les dérivations 2 et 3, mais encore dans les dérivations précordiales V2 et V3 où l'amplitude atteignit 0,4 millivolts.

Dans un cas de coeur pulmonaire grave secondaire à une tuberculose pulmonaire, on nota en plus d'une onde P en pic dans la dérivation 2, des altérations en série dans les dérivations V2 et V3, avec augmentation des ondes P jusqu'à 0,3 millivolts dans ces deux dérivations.

En l'absence d'autre cause, l'onde P en pic dans les dérivations précordiales droites peut servir à confirmer le diagnostic de coeur pulmonaire grave.

La variabilité de la forme, de la dimension et de la direction des ondes P au cours d'une maladie prolongée se trouve démontrée dans plus d'un cas, en particulier dans le coeur pulmonnaire chronique dû à l'emphysème pulmonaire.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

Bei ausgeprägter Vergrösserung des rechten Vorhofes infolge Thrombose der Lungenarterien wurden nicht nur erhöhte P-Zacken in Ableitung 2 und 3 beobachtet, sondern auch in den Brustwandableitungen V-2 und V-3, wo die Amplitude 0,4 Millivolt erreichte.

Bei schwerem cor pulmonale als Folge einer Lungentuberkulose wurde zusätzlich zu einer hohen P-Zacke in Ableitung 2 reihenweise Veränderungen in den Ableitungen V-2 und V-3 beobachtet mit einem Anstieg in den P-Zacken bis 0,3 Millivolt in diesen beiden Ableitungen.

Beim Fehlen anderer Ursachen kann die stark erhöhte P-Zacke in dem Brustwandableitungen über der rechten Seite des Herzens als ein bestätigendes Zeichen eines schweren cor pulmonale dienen.

Die Veränderlichkeit in Gestalt, Grösse und Richtung des P-pulmonale während einer protrahierten Erkrankung wird an einem landläufigeren Fall dargestellt, nämlich einem cor pulmonale infolge eines Lungenemphysems.

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Endocavitary Aspiration in the Treatment of Lung Abscess*

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The endocavitary aspiration, used for the first time in 1938 in the treatment of tuberculous cavities, has gotten into the therapy of lung abscess, with a slow but ever growing rhythm.

In the following Table may be seen the cases known and published from 1939 to 1951.

Year Authors	Number of cases treated	Result
1939—Tarantola (*)	1	Recovery
1941—Grass (*)	4	Recovery
1941—Toury, Vicaire, Maury (*)	1	Recovery
1942—Rosenbloom and Guggenheim (*)	1	Recovery
1942—Effemberger (†)	3	Recovery
1943—Brunner (†)	2	Recovery
1944—Santy and Berard (†)	1	Recovery
1945—Lemainissier and Fourestier (*)	1	Recovery
1946—Marconi (*)	1	Recovery
1946—Scarpa (*)	2	Recovery
1946—Nuti (*)	1	Recovery
1946—Marini (*)	1	Recovery
1947—Nelson (*)	10	Recovery
1948—Viviani (*)	1	Recovery
1948—Mory and Menut (*)	1	Recovery from the abscess. Deceased subsequently after purulent meningo-encephalitis
1948—Casal (*)	4	Recovery
1949—Bikfalvi (*)	20	Recovery
1950—Lopez and Sendon (*)	5	Definite recovery in three cases
1951—Bikfalvi (†)	28	24 successful cases, 4 deceased

(*)—Quoted by Tanzi in "Arch. di Tisiol." 5:540, 1951.
(†)—Quoted by Bikfalvi in "Arch. di Tisiol." 6:1015, 1951.
The total number of cases is 89 with 83 recoveries (93 per cent).

In our Institute in Naples, one department is reserved for the study and application of the aspiration method. The applications in pulmonary abscesses have been performed by Monaldi, Marconi, Tanzi, Babolini, De Marco and by Ceriana in the Hospital of Varese, following our instructions.

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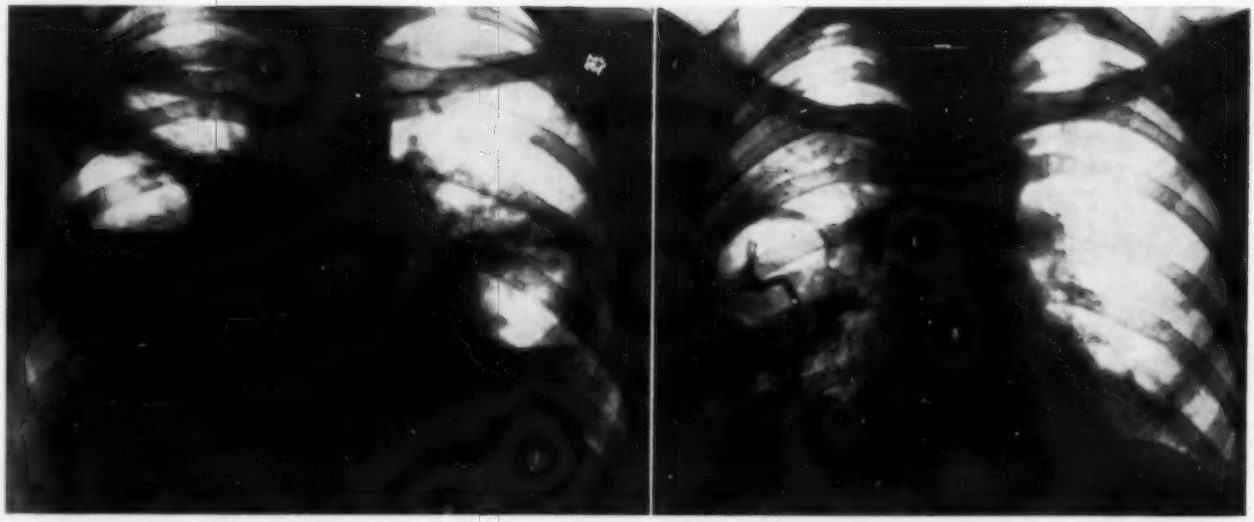

FIGURE 1

FIGURE 2

B. BRUNA—37 years old. *Figure 1:* Bilateral abscess cavities; very serious general condition. *Figure 2:* On February 23, 1953, endocavitary aspiration on the right side. General condition improved, first slowly, then rapidly.

FIGURE 3

FIGURE 4

B. BRUNA—37 years old. *Figure 3:* Two months later, the left abscess is healed up; on the right a small residue is still showing. After three months the sound is taken off. *Figure 4:* Control within five months after recovery. The two lungs appear in full brightness. On the right side a scar-thickness persists.

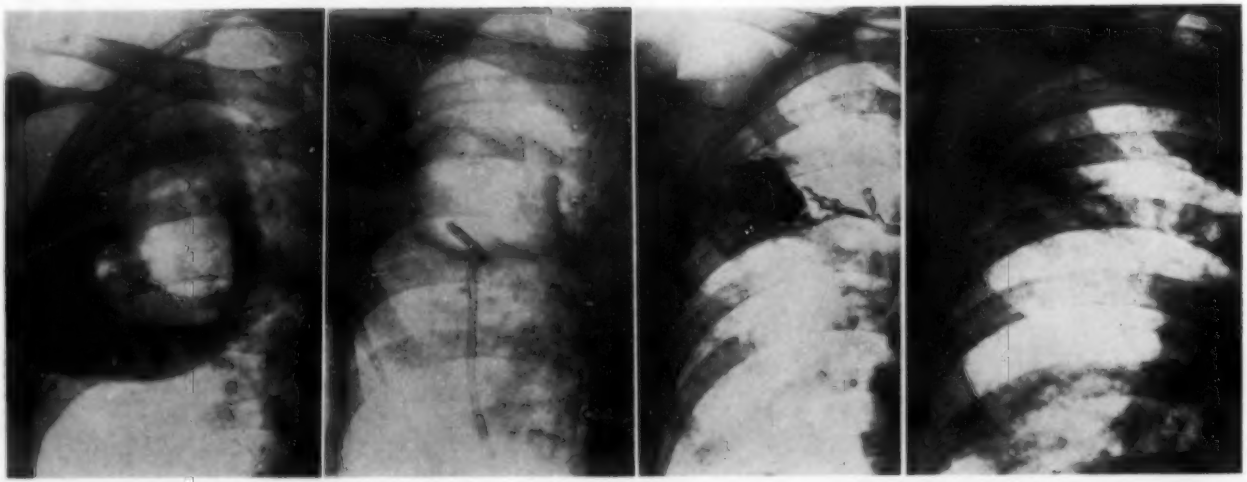

FIGURE 5A FIGURE 5B FIGURE 6A FIGURE 6B

C. GIOVANNI—46 years old. *Figure 5:* Putrid abscess of the right lung, upper lobe. (A) Very serious general condition. Intervention with endocavitary aspiration April 30, 1953: 400 cmc. of pus are extracted. (B) Disappearance of toxic manifestations and of sputum within the first four days. *Figure 6:* After 35 days, the abscess cavity visualized with lipiodol is but a small residue. (A) Some days later the sound is removed because of recovery. (B) Control within three months. A linear scar is the only residue of the former process. The lung has resumed its normal brightness.

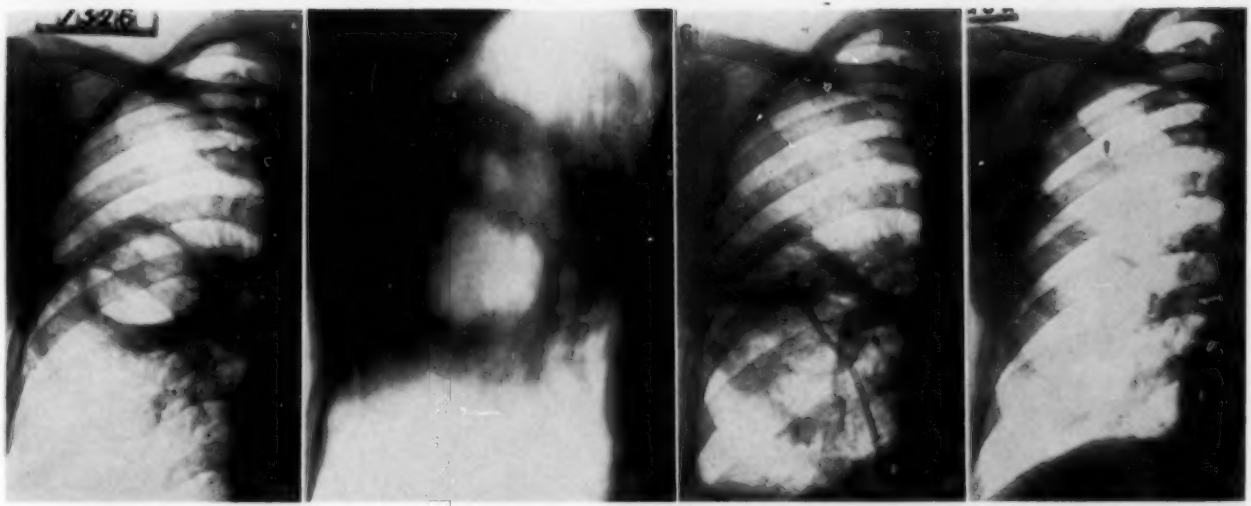

FIGURE 7A FIGURE 7B FIGURE 8A FIGURE 8B

D. B. TEODOSIO—34 years old. *Figure 7:* A and B. Putrid abscess: serious general toxic manifestation: foul purulent expectoration 250-450 cmc. a day. *Figure 8:* Endocavitary aspiration on April 17, 1949, after an antibiotic general treatment of a week. On the third and fourth day, falling of temperature, complete absence of cough and expectoration. (A) X-ray study on the 13th day of treatment—removal of the sound on the 35th day, because of recovery. (B) X-rays taken 13 months after recovery.

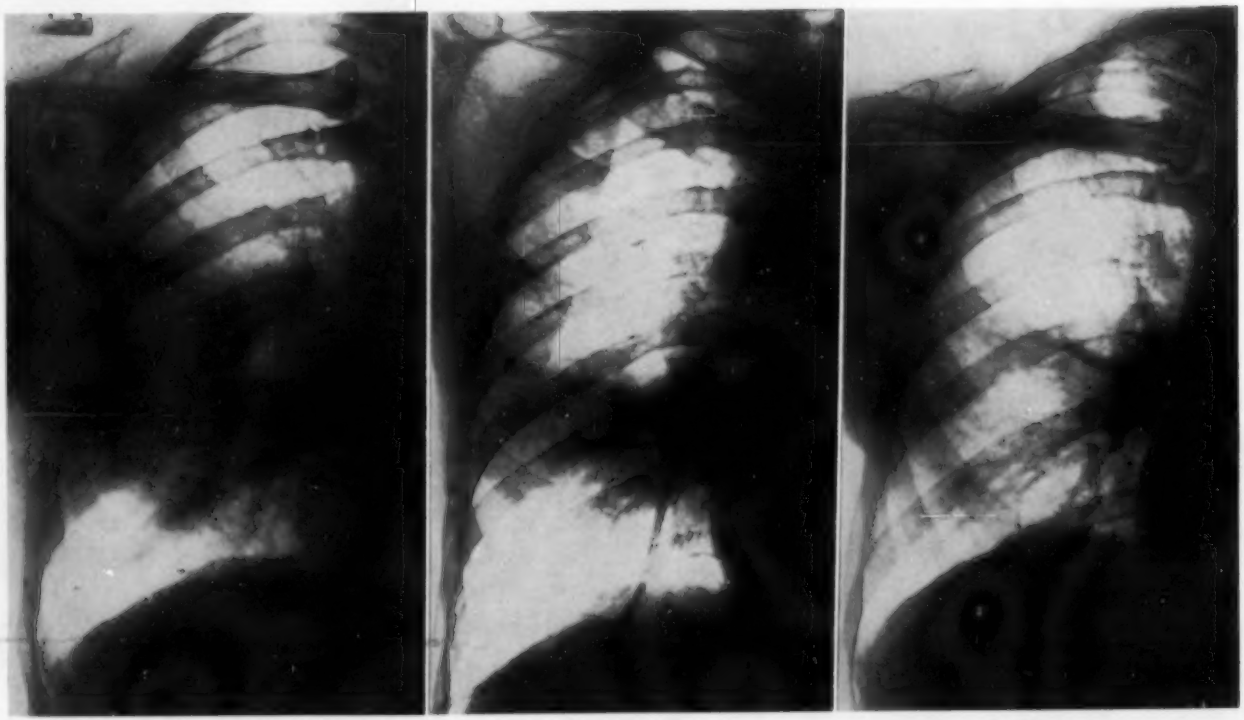

FIGURE 9A FIGURE 9B FIGURE 9C

P. DOMENICO—55 years old. *Figure 9:* Lung abscess of inferior right lobe. (A) With acute general involvement (X-ray July 24, 1954). Intervention with endocavitary aspiration. (B) The procedure continued for 50 days and was followed by recovery. (C) X-ray films October 11, 1954.

The total number of cases is 38, with 33 recoveries (87 per cent) and five failures.

The failures are due to: *one* to fatal haemoptysis during treatment; *one* to inefficiency of the treatment in a serious lobular pluricavitary process; *three* to relapses into chronic abscesses in bronchiectatic patients.

The various pathological stages and the course of the treatment in patients, who recovered, may be shown by some examples.

Examples include all varieties of abscess cavities. Technic of intervention and the way of treatment do not differ from those used in the suction drainage of tuberculous cavities. Treatment, as a rule, was accompanied in the first week with local antibiotic application through the sound.

About the course and the results we may notice: the treatment has lasted, accordingly, from 15 days to three months: even after a few days, all toxic manifestations, cough and purulent expectoration, disappear; the liquid matter, drained by the sound, turned into serous liquid within one to three weeks; together with the cavitary space reduction, one gets the increased translucency of the surrounding tissue and the thinning of the cavitary walls; after a full cleansing of the cavitary walls and the disappearance of the space, a few more days of treatment are needed to get definite recovery.

Late recoveries may be seen in the radiograms either as small thick linear images, or as small scar-knots.

At present in our clinical department reserved to nontuberculous diseases of the chest, endocavitary aspiration is applied in abscess cavities after a general and endobronchial antibiotic treatment. Results appear to be still quicker.

Personal experience on more than 2000 cases of tuberculous cavities treated with endocavitary aspiration has taught us the importance of mechanical factors. The obliteration of the cavity and the exclusion of the draining bronchi are essential conditions in order to reach recovery from tuberculous cavities. Relapses after treatment are always accompanied with the reopening of the bronchi and with the recurrence of the cavitary space.

In abscess cavities, things proceed quite differently. As soon as aspiration modifies the infectious process, the whole picture undergoes an important transformation: the complete cleansing of the cavitary walls, in many a case, appears as sufficient to lead to disappearance of the abscess cavity and later to healing. Mechanical factors have a subordinate position: they operate as far as there exists an infectious process.

Such a different position of the mechanical factors in the tuberculous cavities and in the abscess cavities is confirmed by other elements: the obliteration of a tuberculous cavity through pneumothorax and through surgical-collapse is generally a forward step towards recovery. On the contrary, the author who formerly experimented with collapse-therapy in abscess cavities, proved that an early closing of the cavitary space, with retention of pathological material, caused an aggravation of the process;

in the present practice, antibiotic treatment either by endobronchial or by transparietal ways may give recoveries of abscess cavities in a high percent of cases; on the contrary similar methods are ultimately quite inefficient in tuberculous cavities; the endocavitary aspiration in tuberculous cavities is terminated, nowadays, with a long and complex treatment in order to exclude the draining; no author ever set such a problem for abscess cavities.

All we have been saying agrees with the conception that cavitary space and draining bronchi represent elements of high pathological importance with regard to tuberculous cavities; while, on the contrary, in abscess cavities the preeminent element is the infectious process.

Such a conclusion ought to have a practical inference.

There is no proper and more suitable measure than endocavitary aspiration for the pathological materials of an abscess cavity, and at the same time to extinguish the infectious process. Still, the use of such a method is greatly limited. Some of the reasons for such a limitation are real indeed, that is to say, they are inherent to the nature of the process.

Pulmonary abscesses assume multiform aspects; rather seldom do they form such a cavity as to allow an aspirative intervention; often thickness of the abscess wall, irregular atelectasies, connective tissue invasion complicated the situation, that can only be mastered through an excisional surgical intervention. There are, besides, different reasons due to the deficient knowledge of such a method.

Our school, through the work of so many collaborators has given either solid scientific basis to endocavitary aspiration or easy means and exact direction for its application.

The results thus published and the observations presented in my report offer the certitude that such a method can find a greater use also in the treatment of cavities.

SUMMARY

The endocavitary suction drainage, introduced by the author in 1938 for the therapy of tuberculous cavities, has been later adapted to the treatment of other pathological cavities of the lungs and particularly for abscess cavities.

The medical literature does since 1938 record 89 cases of lung abscesses treated with the endocavitary suction, a large percentage of which have been healed.

The author reports on a new group of patients suffering from serious forms of lung abscess both unilateral and bilateral, in whom the suction drainage, combined with the use of antibiotics, has brought about in a short time complete recovery.

RESUMEN

La succién endocavitaria introducida por el autor en 1938 para el tratamiento de la cavidad tuberculosa se ha adaptado más tarde al tratamiento de otras cavidades patológicas en el pulmón y particularmente a los abscesos.

La literatura médica relata 89 casos desde 1938, de abscesos del pulmón tratados con succión endocavitaria, habiendo curado un gran porcentaje.

El autor presenta una nueva serie de enfermos que sufrían serias formas de abscesos del pulmón tanto unilaterales como bilatera les en los que la succión combinada con antibióticos ha producido una rápida recuperación.

RESUME

Le drainage par aspiration endocavitaire, que l'auteur fit connaitre en 1938 pour le traitement des cavernes tuberculeuses, a été plus tard adapté au traitement des autres cavités pathologiques des poumons, et en particulier des abcès.

La littérature médicale depuis 1938 compte 89 cas d'abcès pulmonaires traités par aspiration endocavitaire dont un large pourcentage a été guéri.

L'auteur rapporte une nouvelle série de malades, atteints de formes sérieuses d'abcès pulmonair, unilatéral ou bilatéral, chez lesquels l'aspiration endocavitaire, associée à l'utilisation d'antibiotiques, a permis une guérison complète en très peu de temps.

ZUSAMMENFASSUNG

Die Saugdränage von Höhlenbildungen, die der Verfasser im Jahre 1938 zur Behandlung tuberkulöser Kavernen einführte, ist später in der Therapie anderer krankhafter Höhlenbildungen in der Lunge, besonders von Abszesshöhlen, angewandt worden.

Im medizinischen Schrifttum seit 1938 finden sich 89 Berichte über mit Höhlensaugdränage behandelte Fälle von Lungenabszess; ein grosser Prozentsatz davon kam zur Heilung.

Der Verfasser berichtet über eine neue Gruppe von Kranken mit schweren Formen einseitiger und beiderseitiger Lungenabszesse, in denen die Saugdränage unter gleichzeitiger Behandlung mit Antibiotika in kurzer Zeit zu völliger Wiederherstellung führte.

Artificial Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis: A Clinical Study

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While artificial pneumoperitoneum has been employed in the treatment of intestinal tuberculosis for over 50 years, it was not until 1933 that its therapeutic value was fully appreciated in the management of pulmonary tuberculosis.

It was Banyai,[2] in this country who first advocated its extensive clinical use, but up to the present date its value in pulmonary tuberculosis is still controversial.

Since the proper place of pneumoperitoneum in pulmonary tuberculosis has been held in question by many, we have attempted through this study to evaluate our own experience with the procedure on the Tulane service of Charity Hospital of New Orleans. There are those who are staunch advocates of its use in nearly all cases of tuberculosis, and there are still other physicians who have given it a trial and discarded it in favor of surgical procedures.

It is well to remember that in the treatment of pulmonary tuberculosis there will always be some patients who will recover no matter what form of therapy is used and pneumoperitoneum in such cases will almost surely help the majority. On the other hand there will be those patients, whom we refer to as "last resort" cases, who are clinically and roentgenologically far advanced and in whom other types of collapse therapy (especially pneumothorax) or surgery are contraindicated, and in most of them pneumoperitoneum is surely doomed to fail. So in the evaluation of the procedure it is essential to take into consideration a number of variables, namely, type of lesion (exudative, fibrotic, mixed), extent of lesion (minimal, moderately advanced, far advanced), location (upper ⅓, lower ⅔ or both upper and lower areas), duration of treatment and supplemental therapy.

The six year period from June 1, 1945 through June 1, 1951 was selected for our study during which 173 cases of pulmonary tuberculosis received pneumoperitoneum. The cases were approximately evenly divided between the two races, with 85 whites and 88 Negroes, and females slightly outnumbered males, 94 to 79. The age of the patients merely reflected the age incidence curve of pulmonary tuberculosis with slightly more than half of the cases occurring between 20 and 40 years, and most of the remainder being beyond 40.

The largest number of cases induced in one year was 60 in 1949-1950. (Table I)

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TABLE I

Number of cases of artificial pneumoperitoneum in the six year period June 1, 1945 through June 1, 1951 (Tulane Tuberculosis Service, Charity Hospital).

1945 - 46	7
1946 - 47	15
1948 - 49	25
1949 - 50	60
1950 - 51	42
Total	173

Of the original 173 cases, only 90 (52 per cent) were considered complete enough for evaluation and analysis. The remaining 83 were considered incomplete because of lack of follow-up after hospital discharge, or inability to locate the roentgenograms of the hospitalization period. These 90 cases were treated with pneumoperitoneum alone, or with pneumoperitoneum and phrenemphraxis either with or without antibacterial drugs. The operation of phrenemphraxis consisted of crushing one or the other phrenic nerve so as to paralyze the corresponding diaphragmatic leaf for usually from six months to one year. The antibacterial drugs consisted of one gram streptomycin twice weekly for a minimum of 42 doses, usually supplemented by 12 grams sodium para-amino-salicylate daily.

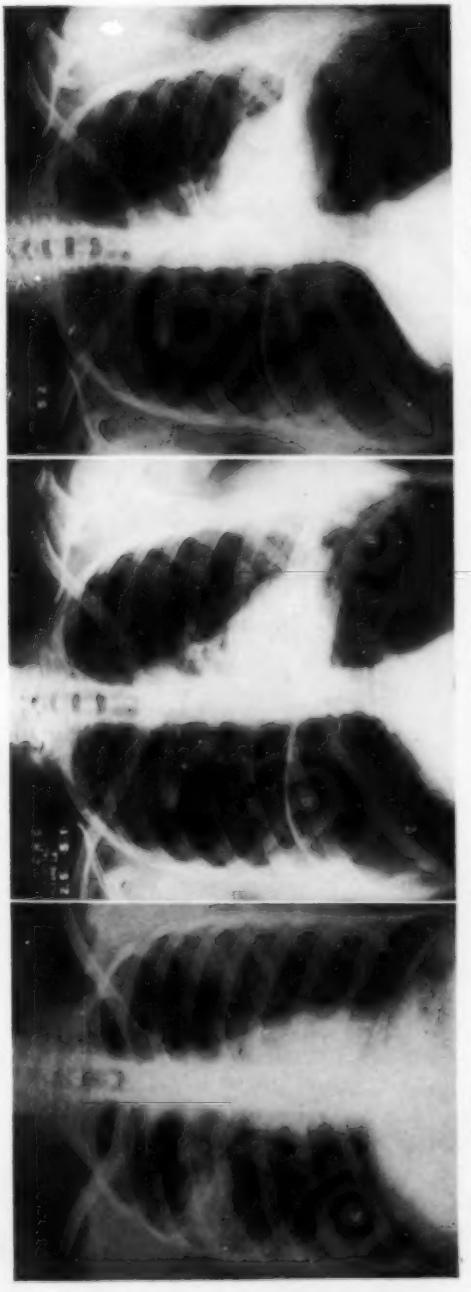
Of the 90 completed cases, 40 were white and 50 were Negro. The type of lesion was classified as predominantly exudative, predominantly fibrotic or mixed (exudative and fibrotic). Most of the lesions were exudative (56 cases—50 per cent), five (6 per cent) fibrotic, and 34 (35 per cent) mixed. The lesions were also classified as to extent according to the National Tuberculosis Association criteria and 69 (77 per cent) were far advanced. Bilateral lesions (63 or 70 per cent) predominated over unilateral ones, and the upper third of the lung fields was involved in 54 or (58 per cent) (Table II).

TABLE II

EXTENT AND DISTRIBUTION OF LESIONS

Minimal	Mod. Advanced	Far Advanced	Total
3 cases (3 per cent)	18 cases (20 per cent)	69 cases (77 per cent)	90
Unilateral 27 cases (30 per cent)		Bilateral 63 cases (70 per cent)	Total 90
Upper 1/3	Upper 1/3 and Lower 2/3	Lower 2/3	Total
54 cases (58 per cent)	27 cases (32 per cent)	9 cases (10 per cent)	90

In the earlier years of the study, antibacterial agents (streptomycin and sodium para-amino-salicylate) were not available and these patients received the benefit of pneumoperitoneum alone, usually with unilateral phrenemphraxis. In the later years, almost all received streptomycin, with or without sodium para-amino-salicylate, in addition to pneumo-


CASE 1C
CASE 1B
CASE 1A

peritoneum, and phrenemphraxis became less frequently employed. It is only an occasional selected case where this latter procedure is now used.

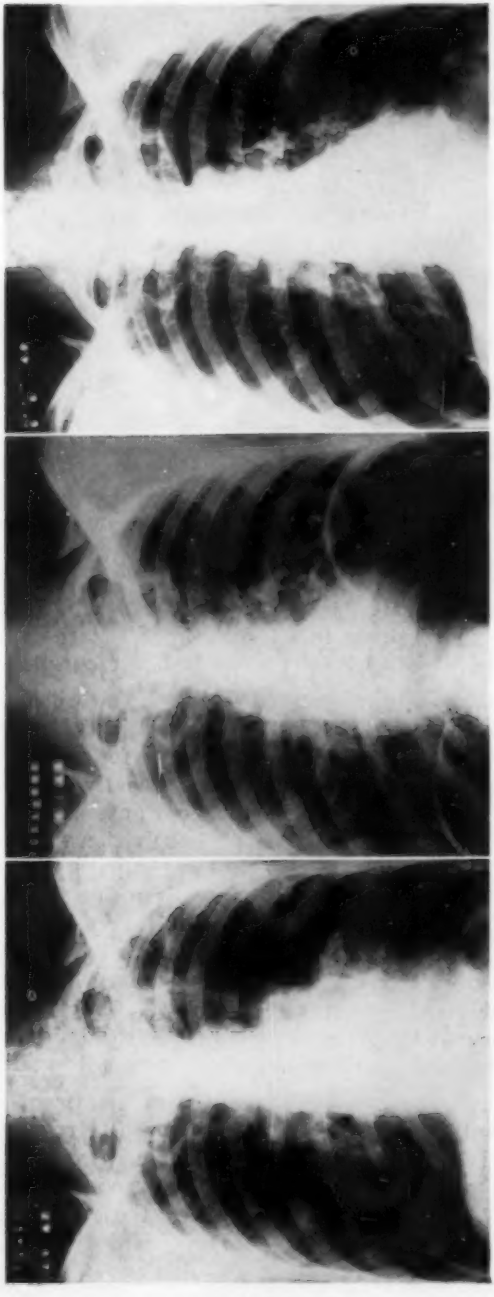
The range of use of pneumoperitoneum was fairly broad and the indications were: 1. definitive therapy; 2. pneumothorax failure; 3. tuberculous pneumonia; 4. holding procedure, until surgery became advisable; 5. last resort.

Those cases of minimal, moderately advanced or far-advanced cases in which pneumoperitoneum was used as a definitive method of treatment comprised that group in which the hospital staff felt pneumoperitoneum was the method of choice of all forms of therapy. The pneumothorax failure group is self explanatory. The group of tuberculous pneumonias is not included in this study and has been reported separately.[11] Those cases of unilateral cavitary disease where surgery is indicated but the patient's condition did not allow the procedure at that time, have been given pneumoperitoneum as a temporizing or holding procedure, usually for at least eight to 12 months. These cases comprise the fourth indication. And the last group embraces those with far advanced, bilateral cavitary disease where surgery is inadvisable due to low pulmonary reserve or poor risk, and other forms of collapse therapy are contraindicated. In this last group, pneumoperitoneum was actually used as a "last resort" procedure for the sake of offering the patient something in addition to bed rest. We do not advise administering pneumoperitoneum routinely in all such cases but these last ones were so grouped in order to evaluate the effect of pneumoperitoneum.

The overall results of pneumoperitoneum were classified as IMPROVED (inactive or arrested NTA classification 1950), ACTIVE, retrogressing, ACTIVE, progressing or DEAD. The criteria used for IMPROVED were (1) all cavities closed, (2) sputum converted to negative by concentrate (arrested) or by culture (inactive). The number of cases in which the sputum was cultured was so small that a separate subdivision was deemed unnecessary and so the larger group IMPROVED was utilized. The ACTIVE group included those which did not fulfill the requirements for the IMPROVED group, and in which the lesions were retrogressing or progressing. Retrogression implied closure of some but not all the cavities, reduction in cavity size, extensive clearing of the pulmonary infiltrative lesion and sputum which was either negative or positive. Progression implied that there was no benefit to either the cavities or the infiltration, the lesion had increased in extent and the sputum was usually positive.

Using these criteria, the overall results of treatment can be stated. Of the 90 treated, 35 were improved, 12 active retrogressing, 24 active progressing and 19 dead. Considering the first two groups together as including those who were improved or improving, the figures would incidate that 47 were in this category and the remainder (43) either dead or on a downhill course (Table III).

These results are similar to those reported in other studies for a comparable period of follow-up.[1, 2, 4, 5, 7, 10, 13]



CASE 2C

CASE 2B

CASE 2A

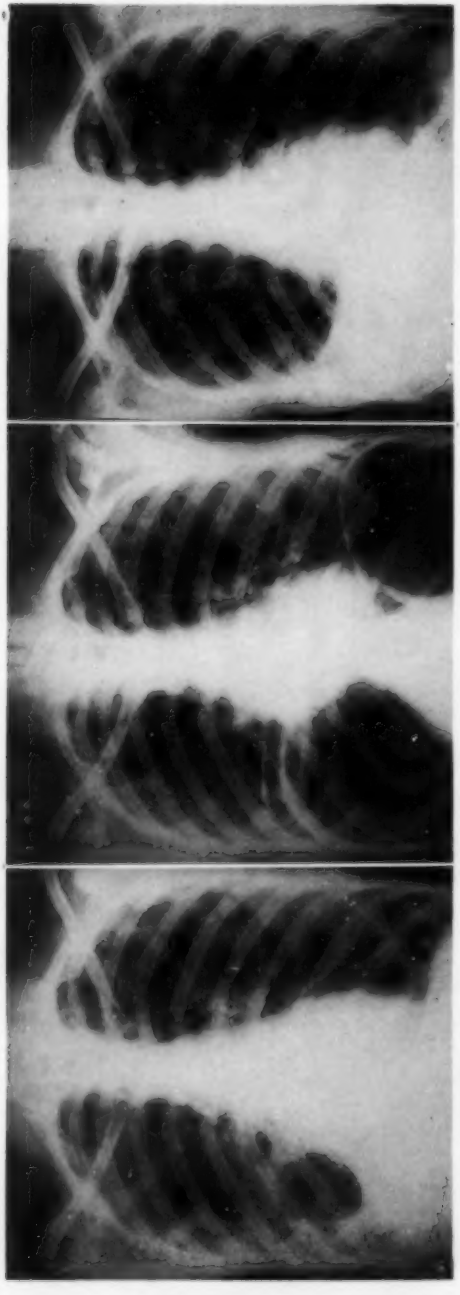
When the group as a whole is analyzed from the standpoint of whether or not antibiotics were used, it will be noted that the results were better in the group receiving pneumoperitoneum and antibacterial agents than in the group on pneumoperitoneum alone (Table III). There were eight out of 26 (30.7 per cent) showing improvement on pneumoperitoneum alone. When pneumoperitoneum is combined with streptomycin alone, 10 out of 26 cases (38.5 per cent) were improved. When it was combined with streptomycin and PAS the improvement was even greater. There were 17 of a total of 38 cases improved (45 per cent). In the eight improved cases who received pneumoperitoneum alone there were six with cavitary disease whose cavities closed. This illustrates that pneumoperitoneum alone is capable of closing cavities and Case Summary 2 is such an example. On the other hand, of a total of 16 treated by pneumoperitoneum alone who were active progressing or dead, almost all (14 cases) had cavitary disease. It is apparent that pneumoperitoneum alone is capable of benefiting cavitary disease and this occurred in 30 per cent of the cases.

TABLE III

RESULTS OF THERAPY (ALL CASES)

	Improved (Inactive or arrested)	Active (Retrogressing)	Active (Progressing)	Dead	Total
Minimal	2	1	0	0	3
M. A.	13	1	3	1	18
F. A.	20	10	21	18	69
Total	35	12	24	19	90
Cases treated with Pneumoperitoneum alone (No Antibacterial Agents)					
Minimal	0	1	0	0	1
M. A.	3	1	2	0	6
F. A.	5	0	3	11	19
Total	8	2	5	11	26
Cases treated with Pneumoperitoneum and Streptomycin					
Minimal	2	0	0	0	2
M. A.	4	0	0	1	5
F. A.	4	4	4	7	19
Total	10	4	4	8	26
Cases treated with Pneumoperitoneum, Streptomycin and PAS					
Minimal	0	0	0	0	0
M. A.	6	0	1	0	7
F. A.	11	6	14	0	31
Total	17	6	15	0	38

A breakdown of our cases with regard to presence or absence of cavities reveals that of the 69 far-advanced cases all but one had cavities, ranging in size from small honeycomb areas to giant cavities exceeding 8 cm. in diameter. Of these 68 cases with cavities, 30 were improved or improving, representing an improvement percentage of 44. Of the 18 with moderately advanced disease, six had cavities of whom four (66 per cent) were considered improved (Table IV). In the smaller group with no cavities, totaling 16, 81 per cent evidenced an improved or improving status (Table IV).



CASE 3C

CASE 3B

CASE 3A

In a study done by Barnes and Barnes[12] to determine the fate of cavitary tuberculosis in cases on bed rest and supportive measures (without collapse or antibiotics) among the 1454 cases reviewed, 80 per cent died within one year and 95 per cent died within 15 years. The average duration of life of all cases was about 12 months. In our cases of cavitary disease (74 cases) treated with pneumoperitoneum or pneumoperitoneum and antibiotics, 25 per cent (19 cases) were dead at the end of one year. The mortality at the end of one year was 58 per cent in cavitary cases receiving only pneumoperitoneum, 36 per cent in cavitary cases receiving pneumoperitoneum and streptomycin, and no mortality in those receiving pneumoperitoneum, streptomycin and PAS. All of these deaths except one were far advanced cases. About half (11) of those who died had received only pneumoperitoneum (and 7 of this group received it for less than nine months) and the remaining seven received pneumoperitoneum and streptomycin.

TABLE IV

Results of Therapy of Cavitary Disease

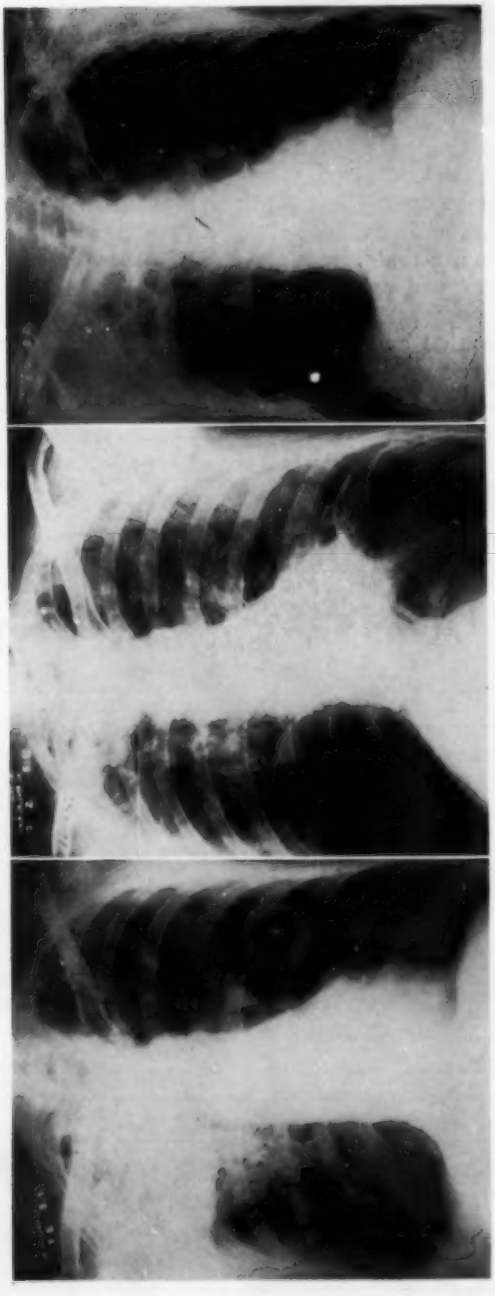
	Improved	Active (Retrogressing)	Active (Progressing)	Dead	Total
M. A.	4	0	1	1	6
F. A.	20	10	20	18	68
Total	24	10	21	19	74
Results of Therapy of Non-Cavitary Disease					
Minimal	2	1	0	0	3
M. A.	9	1	2	0	12
F. A.	0	0	1	0	1
Total	11	2	3	0	16

There were nine with the disease process limited to the lower two-thirds of the lung field, of whom six were improved, two active retrogressing and one dead. This represents a much higher percentage (66 per cent) of improved cases than that seen in the group as a whole. Although the total number of cases (nine) is small, it tends to confirm the widely held belief that pneumoperitoneum is particularly useful in lower lobe disease. This is of some importance when it is realized that lower lobe tuberculosis is a type of lesion which is usually difficult to treat. The one who died had had diabetes mellitus for 10 years prior to treatment. Of the two which are active and retrogressing, one received no antibiotic and the other less than 14 Gm. of streptomycin. Two of the improved cases had cavities and

TABLE V

Results of Therapy According to Race

	Improved		Active Retrogressing		Active Progressing		Dead		Total
	W	C	W	C	W	C	W	C	
Minimal	0	2	11	0	0	0	0	0	3
M. A.	7	6	0	1	0	3	0	1	18
F. A.	11	9	6	4	9	12	7	11	69
Total	18	17	17	5	9	15	7	12	90



CASE 4C

CASE 4B

CASE 4A

received no antibiotic and the remaining four improved cases had cavities and received 18 Gm., 41 Gm., 42 and 60 Gm., of streptomycin.

Table V is a representation of results of therapy with regard to the two races. There was a greater percentage of improvement in whites than in Negroes, 61 per cent and 45 per cent respectively. A larger percentage of Negro than white patients either died or showed progression. This confirms the general belief on our service that Negroes in general do worse when they develop tuberculosis than whites, irrespective of therapy employed.

The results of treatment as applied to the patients grouped according to indication is simply another way of showing that our series of cases was saturated with those who had far-advanced disease who would do poorly on any treatment. The most unfavorable results are in the "last resort" group, these being far-advanced, bilateral cavitary disease where any other treatment was contraindicated and pneumoperitoneum was used to keep the patient under close supervision and observation (Table VI). It is our impression that in this type of case pneumoperitoneum has little to offer.

TABLE VI

Indications	Improved	Active Retrogressing	Active Progressing	Dead	Total
Def. Treatment	22	4	5	2	33
Pnx. Failure	7	1	2	2	12
Holding Procedure	4	0	5	2	11
Last Resort	2	7	12	13	34
Total	35	12	24	19	90

The duration of pneumoperitoneum in all 90 cases varied from three to 60 months. There were eight in whom the duration of pneumoperitoneum was less than nine months and all had unfavorable results. Seven are dead and in all pneumoperitoneum was used as a last resort. One case is ACTIVE progressing, and in this case pneumoperitoneum was used as a definitive measure. The average duration of pneumoperitoneum in the IMPROVED group was approximately *two years* (23.7 months). It was noted in those in whom improvement was to be found, that clearing of the exudative component and closure of the cavities appeared within eight or nine months (average 8.6 months) after the induction of pneumoperitoneum. It was apparent that by that period of time one could form an opinion as to whether the disease process was actually responding to treatment. It is now felt on our service that once pneumoperitoneum is begun it should be continued for at least nine months before deciding to abandon it. The average time for conversion of the sputum to negative was 11.4 months after initiation of pneumoperitoneum.

Pneumoperitoneum was apparently a safe and easy procedure in this series. Complications were few and of seemingly little consequence. Abdominal discomfort was occasionally noted but to no great extent. The only complication of real significance was ascites which occurred in only

five of the 173 cases. Of the five with ascites, three required paracentesis on several occasions and then pneumoperitoneum was continued uneventfully. In the other two, it was necessary to discontinue pneumoperitoneum. In one of whom, the fluid contained acid-fast bacilli.

Illustrative of the various types of cases of pulmonary tuberculosis in which pneumoperitoneum was used effectively, the following are presented.

Case 1: M. D., 18 year old white female was admitted on September 19, 1950 complaining of fatigue, cough and loss of weight. Initial roentgenogram of September 21, 1950 revealed bilateral exudative lesions involving the upper thirds of both lung fields. She was begun on streptomycin (1 Gm. twice weekly) and PAS (12 Gm. daily) on September 29, 1950 and received a total of 60 Gm. of streptomycin up to December 22, 1950. Pneumoperitoneum was begun on October 6, 1950 and has been continued to date. The lesion on left resolved with a small residual scar by November 1950 and right lesion was stable (hard and contracted) by August 1951. Sputum cultures have been negative for acid-fast bacilli since September 1951. By March 7, 1952, both lesions were still stable.

Comment

In this case of bilateral tuberculosis, pneumoperitoneum was used as a definitive means of therapy in conjunction with the antibiotics and bed rest. It is difficult to know how much pneumoperitoneum contributed to the arrest of this case, for she may have recovered on bed rest and antibiotics alone.

Case 2: R. S., a 50 year old Negro male was admitted on September 8, 1947 because of malaise, lassitude, afternoon fever, night sweats, cough and pain in the left chest for four months. His initial roentgenogram of August 29, 1947 revealed a far-advanced, mixed lesion involving the upper third of each lung with a large 5.5 cm. cavity in the left subapex. Pneumoperitoneum was begun on October 17, 1947 and continued through September 27, 1948. Left phrenemphraxis was done on December 5, 1947. He received no antibiotic. No cavity was evident by February 16, 1948. The film of September 1, 1948 here illustrated is essentially the same as the one of February 16, 1948. A stable residue has replaced the cavity in the left subapex and the right side has become stable as well. The lesions were unchanged up to pril 7, 1952. Sputum cultures were negative in June 1951.

Comment

This case of far advanced cavitary tuberculosis showed closure of the cavity in four months under pneumoperitoneum supplemented by ipsilateral phrenemphraxis. Antibiotics were not used.

Case 3: A. M., a 20 year old colored female was admitted on February 17, 1948 with constitutional symptoms of malaise, fever and night sweats for four months. The initial roentgenogram of November 28, 1947 revealed a far advanced mixed lesion with two large cavities in the lower two-thirds of the right lung. Pneumoperitoneum was begun on March 4, 1948 and continued to February 25, 1949. Right phrenic crush was done on May 24, 1948, avulsion of the nerve on April 9, 1949. Streptomycin was given from March 22 to April 9, 1949, a total of 18 Gm. The large cavity remained patent up to March 1949 when it was decided to do right lower lobectomy. Sputum was converted to negative on July 26, 1949 and has remained so to date.

Comment

This case represents failure of pneumoperitoneum to close a large lower lobe cavity, after a trial of 12 months. Surgery was necessary to effect removal of the cavity.

Case 4: L. S., a 43 year old white male was admitted on December 20, 1949 because of cough, hemoptysis and fever of one week's duration. His initial roentgenogram of February 15, 1951 revealed far-advanced, exudative disease involving the upper one-half of right lung. Pneumoperitoneum was begun on April 30, 1951 and continued to March 1952. Right phrenic crush was done on April 27, 1951. Streptomycin, 1 Gm.

twice weekly, and PAS, 12 Gm. daily, were given from January 18, 1951 to February 28, 1952, a total of 112 Gm. streptomycin being given. The cavity persisted in the right upper lobe and sputum remained positive. In March 1952 modified thoracoplasty (Paulino type) was done on the right side. Sputum was negative by culture since August 22, 1952 and he is improved to date.

Comment

This patient's exudative component resolved, leaving in the cleared area a right upper lobe cavity which failed to close on pneumoperitoneum, necessitating surgical intervention.

SUMMARY

1. A six year series of tuberculosis patients receiving pneumoperitoneum was reviewed and 90 cases were analyzed. Pneumoperitoneum was used alone, with phrenemphraxis and with antibacterial drugs.

2. The lesions were predominantly exudative, far-advanced, bilateral cavitary and in the upper one third of the lung.

3. Pneumoperitoneum proved to be of definite value with regard to cavity closure and its therapeutic effectiveness was enhanced by antibiotics (streptomycin and sodium para-aminosalicylate).

4. Response to therapy was usually evident by the ninth month of pneumoperitoneum, and this should be the minimum duration of therapy once begun.

5. Complications from pneumoperitoneum are few; ascites and abdominal discomfort occasionally caused the procedure to be discontinued.

RESUMEN

1. Una serie de enfermos tratados durante seis años con neumoperitoneo se revisa y se analizan 90 casos. El neumoperitoneo por tuberculosis fué usado solo, con frenopraxis y con drogas antibacterianas.

2. Las lesiones fueron predominantemente exudativas, muy avanzadas cavitarias bilaterales y en el tercio superior del pulmón.

3. El neumoperitoneo demostró ser de un valor definido en relación al cierre de cavidades y su valor fué acentuado por el uso de antibiótics (Estreptomicina y PAS sódico).

4. La respuesta al tratamiento fué habitualmente evidente alrededor del noveno mes de neumoperitoneo y ésta debe ser la duración máxima una vez empezado.

5. Las complicaciones del neumoperitoneo son pocas; ascitis y molestias abdominales fueron causas ocasionales de interrupción del procedimiento.

RESUME

1. Les auteurs passent en revue les cas de tuberculose observés pendant six ans et ayant été traités par pneumopéritoine. Ils en analysent 90 cas. Le pneumopéritoine fut utilisé soit isolément, soit en association avec la paralysie diaphragmatique, soit avec un traitement antibactérien.

2. Dans la majorité des cas, les lésions étaient secrétantes très avancées, cavitaires, bilatérales, et avaient leur siège dans le tiers supérieur du poumon.

3. Le pneumopéritoine fit la preuve de son efficacité pour amener la fermeture des cavités et son action thérapeutique fut renforcée par les antibiotiques (streptomycine et P.A.S.)

4. La réponse à la thérapeutique apparut nettement en général vers le 9ème mois du pneumopéritoine. Ce temps doit être la durée minimum de ce traitement.

5. Les complications du pneumopóritoine sont peu nombreuses; de l'ascite et des troubles abdominaux peuvent amener la cessation du traitement.

ZUSAMMENFASSUNG

1. Eine 6-Jahresreihe von mit Pneumoperitoneum behandelten Kranken wurde durchgesehen und 90 Fälle näher besprochen. Das Pneumoperitoneum kam zur Anwedung entweder allein, mit Phrenikusquetschung oder mit antibakteriellen Heilmitteln.

2. Die Herde waren vorwiegend exsudativ, weit fortgeschritten, beiderseits cavernös und befanden sich in den oberen Lungendritteln.

3. Das Pneumoperitoneum erwies sich von festbegrenztem Wert hinsichtlich Cavernenverschluss, und seine therapeutische Wirksamkeit erfuhr eine Steigerung durch Antibiotika (Streptomycin und Natrium-para-aminosalicylsäure).

4. Die Reaktion auf die Behandlung trat für gewöhnlich im 9. Monat der Pneumoperitoneum-Therapie in Erscheinung, und diese Zeitspanne muss die Mindestdauer der einmal begonnenen Behandlung sein.

5. Komplikationen durch das Pneumoperitoneum treten wenig auf; Ascites und abdominelle Beschwerden waren gelegentlich der Anlass dafür, mit dem Verfahren aufzuhören.

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Unorthodox Clinical and Roentgenological Features of Pulmonary Embolism

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The subject of pulmonary embolism is certainly not occult. No longer is every postoperative pulmonary complication labeled pneumonia, pleurisy, or heart disease. Its frequency is fully appreciated and the surgeon is quick to institute measures to combat its occurrence. From a preventive standpoint, with the recent tendency to ambulate patients early, he is observing how the incidence of embolism decreases.

In the field of medicine, pulmonary embolism is known to occur none too rarely. Autopsy, time and time again, reveals emboli in the pulmonary circuit, even when none was suspected clinically. This is especially true of cardiacs.

In 1929 I had the opportunity to assist at the necropsies performed in the pathology laboratory of Erdheim at the Spital der Stadt Wien. The number of pulmonary emboli routinely observed was considerable. It was the rule in those cases first to incise the calves of the cadaver transversely and explore the lumina of the deep veins. Notwithstanding the absence of any external evidence of venous obstruction in the limb, loose thrombi in these vessels were frequently present. This was the most frequent site of origin of pulmonary emboli. It is unnecessary to point out that thrombi may also be found in the larger and smaller pelvic veins, and also attached to the endocardium of the heart.

Pulmonary embolism is more common in the bed ridden patient. In various articles on abuse of bed rest, it has been stated that there are few conditions which require absolute confinement to bed for any protracted period of time. Even in coronary thrombosis the patient is advised to move his toes and legs as soon as feasible. Comatose patients are not allowed to remain rigidly immobile in any one position. Senile patients are compelled to get out of bed as soon as they can.

This paper will only emphasize the possibility of embolism in any patient. Three cases admitted to the medical service of Metropolitan Hospital and a private patient are presented. Their unorthodox clinical and roentgenological features are worthy of comment. One had become an invalid by many episodes of embolism over several years and had been treated by various doctors for diverse illnesses. The second had been discharged recently from the armed forces and was sent in as a case of pneumonia. Only when this disease did not resolve under antibiotic therapy was the correct diagnosis perceived. The third presented right sided and then left sided pleurisy on subsequent admissions to the hospital. During the first admission, cough with blood expectoration, swelling of the legs, and tenderness of the calves failed to appear, and no one suspected pulmonary embolism. The private patient had had two attacks of so called

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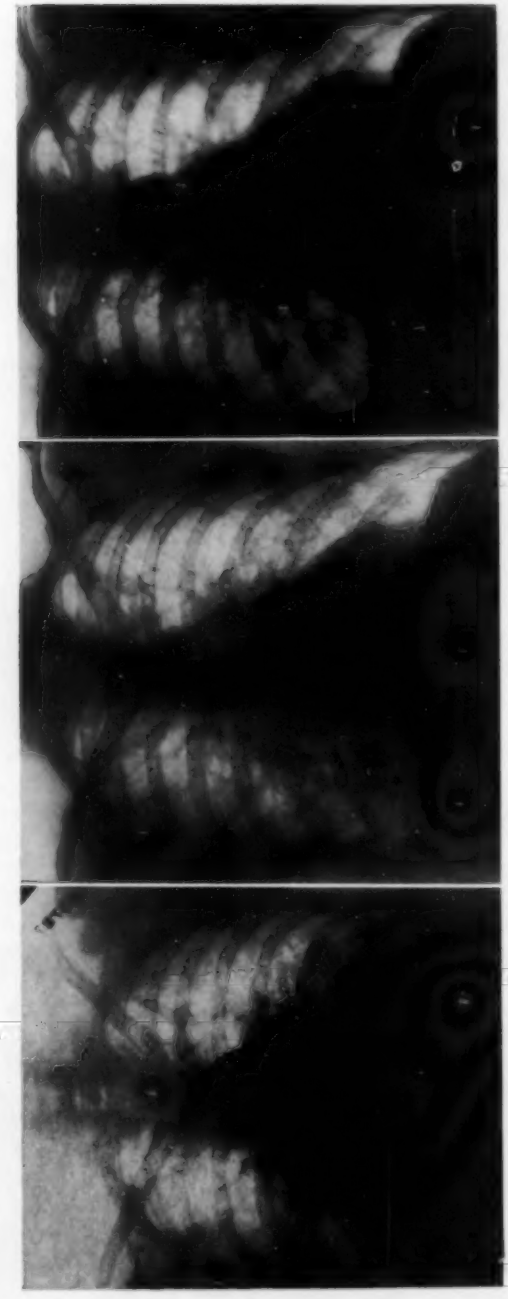

FIGURE 3

FIGURE 2

FIGURE 1

bronchopneumonia, and at the onset of his most recent illness had experienced excruciating precordial pain resembling that of coronary thrombosis.

Review of these cases would suggest that if one expects to find the classical features of embolism, many episodes will be wrongly diagnosed. Since the patient's life may be in jeopardy, this error can be more than of academic interest.

Case 1. J. S. 36 yr. old white male, admitted to hospital on May 4, 1945, with a diagnosis of "toxic" pneumonia. Prior to admission temperature had been 105° F. and he received six gm. of sulfadiazine in 24 hours without favorable response. There was history of pain in the lower left chest aggravated by respiration, cough with expectoration of blood tinged sputum, fever, chills, dyspnea, and severe prostration of one to two days duration. In 1935 there was hospitalization for severe right flank pain and gross hematuria, diagnosed as probable renal calculus. In 1937 he had right sided pleurisy, and this past winter, severe colds. Several days after admission, he also recalled having received injections for varicose veins a few years previously. The history obtained was quite meager because of the extreme toxicity of the patient. When he was well on the road to recovery, he was recognized on the ward by a physician who had treated him for pleurisy in 1937. Since that incident is relevant, it will be gone into later.

X-ray film of the chest showed mottling of both lungs interpreted as bilateral pneumonia (fig. 1). The heart was enlarged and the pulmonic conus prominent. Electrocardiograph revealed right ventricular strain. The liver was palpable. On ausculation P2 was louder than A2. There was a soft systolic pulmonic murmur. A cardiologist thought that a patent interatrial septum defect was a possibility. Sulfadiazine and penicillin were both administered. On May 8, 1945, sulfa was discontinued. The temperature had ranged from 103-105° F. on admission, and on May 17, 1945, had fallen to 99-101° F. He improved generally, but was still slightly febrile. Penicillin was discontinued on May 17, 1945.

On May 23, 1945, his condition deteriorated with gradual rise of temperature. Cardiac decompensation with bilateral hydrothorax was diagnosed. Digitalis was administered and 250 cc. of sanguinous fluid was removed from the right pleural cavity. For the first time the diagnosis of pulmonary infarct appeared on his chart. On May 29, 1945, cough was productive of bloody sputum. Cyanosis and jaundice with a larger, more tender liver were obvious. Penicillin was resumed. On May 31, 1945, bilateral ligation of the common femoral veins was performed. During the operation his condition became grave and exploration of the lumina of the veins was not attempted. Immediately after the operation there was a spectacular change. Temperature dropped to normal and never rose again. On June 6, 1945, penicillin was discontinued. With the exception of moderate edema of the legs, complete recovery quickly took place. The pathological report of the veins revealed chronic phlebitis.

He left the hospital on July 6, 1945. X-ray film on January 4, 1946 (fig. 2) and fluoroscopy on June 12, 1946 were negative except for lower right pleural adhesions. The heart was somewhat enlarged and the conus prominent. The soft systolic pulmonic murmur remained. He stated that he had been particularly healthy. When seen last, one year ago, his health was excellent.

FIGURE 4

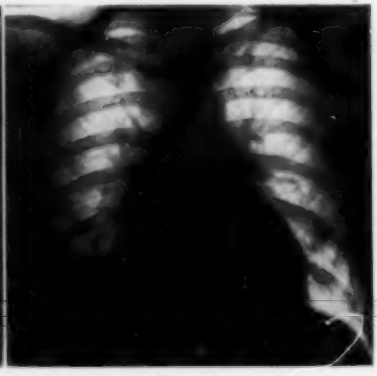

FIGURE 5

FIGURE 8

FIGURE 7

FIGURE 6

It is of great interest to review the past history of pleurisy in 1937. At that time he had had slight cough for two weeks with pain in the lower right chest aggravated by respiration. Temperature was 101° F. X-ray film revealed obliteration of the right costophrenic angle by a small amount of fluid (fig. 3). The same soft systolic pulmonic murmur heard in 1945 was present. Fluid rapidly accumulated and almost the entire thoracic cavity was filled. Unfortunately the x-ray films taken at the hospital were destroyed. On the first occasion 1000 cc. of clear yellow fluid was withdrawn, and a few days later 2,200 cc. Specific gravity was 1016, protein 1 per cent, 230 cells per c.mm., most of which were lymphocytes. Culture was negative. Examination for tubercle bacilli, including guinea pig inoculation, was negative. Following paracenteses, fluid did not reaccumulate, and x-ray film studies concluded: "Pleural effusion diminished in extent due to aspiration. Marked thickening of the hilus shadow is now visible. The possibility of a primary bronchogenic carcinoma of the right lower main bronchus is suggested." The pathological examination of the fluid was just as misleading. The diagnosis was, "transudate, anaplastic carcinoma, grade IV." He made a rapid recovery and was followed after he left the hospital. Except for pleural thickening at the right base, x-ray film was negative. There was slight pain in this region. In October 1937 slight enlargement of the heart was detected. On April 29, 1938, x-ray film (fig. 4) indicated complete clearing of the right lung field. On May 19, 1938, there was right axillary pain low down and a rub was heard. Slight temperature of 100° F. was found. On March 20, 1939, there was pain in the left axilla. On January 13, 1940, he stated that a month previously a left inguinal hernia had been repaired. The day after leaving the hospital the same pain appeared in the right chest. X-ray film on January 13, 1940 (fig. 5) revealed clouding at the right base. A pleural rub was heard. Temperature was 100° F. In two weeks complete recovery had taken place. Except for frequency of upper respiratory infections, this man remained fairly well until his illness of 1945.

He continued to be employed as a chauffeur as he had been for many years. Whether this sedentary occupation played any role in this disease may be considered. One other point which may be quickly commented on is that since the cardiac findings suggested a congenital lesion with a small atrial septum defect as the most likely possibility, is it too far fetched to assume that the "renal calculus" in 1935 was an embolus from a leg vein which accidentally traversed the hole to lodge in the right kidney?

Case 2. I. S. 38 yr. old Puerto Rican male, admitted from another hospital on January 10, 1946, with a diagnosis of tuberculous pleural effusion. Temperature was 103° F. The chief complaint was pain in the left chest. The history was subsequently obtained through an interpreter. The patient had been in the air force three years previously for one and a half years, and had been discharged because of a heart murmur. While in the service he had been hospitalized for two months because of swelling and numbness of the feet. Following his discharge he was well for a few months. After taking a job as a superintendent his feet commenced to swell. No dyspnea was present. He remained in bed for two months prior to admission. On a few occasions blood was expectorated. A few days prior to admission he was acutely ill with chest pain, hemoptysis, and fever.

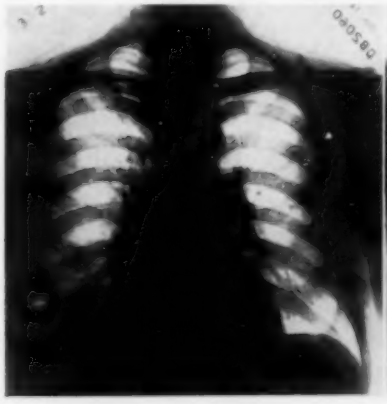

FIGURE 9

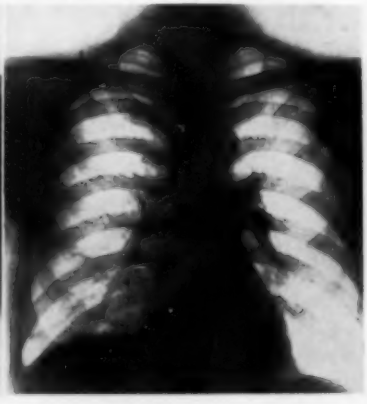

FIGURE 10

At the hospital there were signs of left pleural effusion. A faint systolic murmur was heard at the apex. The heart was enlarged. The liver was enlarged and tender. There was ascites, edema of both elgs, and palpable indurated femoral veins. The various diagnoses considered were tuberculous effusion, pulmonary neoplasm, concates syndrome, pneumonia, and pulmonary embolism with cardiac decompensation. X-ray film on January 11, 1946 (fig. 6) showed left pleural effusion and enlargement of the heart. Sputum was negative for tubercle bacilli. Electrocardiograph showed right ventricular strain. B. P. was 110/80. The temperature was not normal after the 32nd day, notwithstanding sulfonamide and penicillin therapy. On January 18, 1946, thoracentesis produced 1000 cc. of pinkish fluid. The surgical consultants accepted the case and bilateral femoral venous ligations were performed. X-ray films on January 30, 1946 (fig. 7) showed less effusion and on July 2, 1946 (fig. 8) complete resorption. The heart was enlarged and its left border straight. He made an uneventful recovery.

Case 3. A. V. 46 yr. old white chauffeur. Admitted on March 1, 1946, for pain in the right upper quadrant, aggravated by respiration. Temperature was 102° F. X-ray film on March 2, 1946 (fig. 9) showed clouding of the right costophrenic angle. Treatment was with penicillin parenterally. There was clearing on March 8, 1946 (fig. 10). Patient left the hospital the next day. He returned on April 2, 1946, with pain in the left leg. Varicosities of the left leg of many years standing were noted. There had been phlebitis in the past. He signed out April 3, 1946, but returned May 5, 1946, with a temperature of 105° F. He had been having pain in the right chest anteriorly with dyspnea for a few weeks. On May 7, 1946, he experienced pain in the left calf. Electrocardiograph showed S1, inverted T2 and T3, Q3, and right axis deviation, pointing to pulmonary embolus. X-ray film on May 9, 1946 (fig. 11) showed clouding in the region of the right apex. On May 15, 1946, there was pain in the left chest with congestive signs. Bilateral superficial and deep vein ligations were performed. Film of June 3, 1946 (fig. 12) showed clearing, except for residual involvement of the left costo-phrenic sinus. Recovery was uneventful.

Case 4. A. J. 45 yr. old white male who suddenly developed pneumonia with classical physical signs in the right upper lobe in May 1940. He was treated at home with sulfapyridine. Seen at my office two weeks later, fluoroscopy revealed a small shadow in the right upper lung field. Six weeks following, x-ray film showed complete clearing. Sputa were negative for tubercle bacilli.

In March 1950 there was recurrence of this pneumonic episode, and on March 3, 1950, x-ray film (fig. 13) showed infiltration at the base of the right upper lobe. Sputa were again negative.

On May 3, 1950, after being completely well, he was seized with pain below the left nipple while going to work. It grew progressively worse and dyspnea appeared. The physician at his place of work administered morphine, and referred him to Park East Hospital with a diagnosis of coronary thrombosis. There pneumonic signs were found anteriorly to the left of the heart. Electrocardiographs taken then and several times since were normal. Posterior anterior and lateral films of the chest (fig. 14 and fig. 15) were taken on May 4, 1950. X-ray film findings were, "peribronchial pneumonic infiltration in the lower half of the left lung adjacent to the cardiac border. The possibility that the pneumonic change may be due to an infarction should also be borne in mind." This is best exemplified by the lateral view (fig. 15) which demonstrates a wedge shaped shadow in the lingular segment. He left the hospital in a few days and has remained completely well. He is a polisher by trade and stands on his feet a good deal. There has never been any evidence of thrombi in the lower extremity.

In reviewing the histories of patients with embolism, one does not necessarily find the text book symptoms of chest pain, cough with bloody expectoration, dyspnea, jaundice, and the local lower extremity findings of venous thrombi. There are many possibilities when an embolus lodges in a pulmonary vessel. Not all emboli cause infarcts since hemorrhagic consolidation will not take place when there is adequate collateral circulation. With large multiple emboli occluding vessels, death from shock can be instantaneous, but should the patient survive, pulmonary pathology still might not be evident in the face of shock and prostration. Then, too, pulmonary hypertension could develop and death supervene from dilatation and failure of the right ventricle. (In cases 1 and 2 cor pulmonale was present.) Therefore, if the pulmonary pathology has not expressed itself,

treatment solely with digitalis for heart failure might erroneously be administered.

Even if one's attention is directed toward obvious lung involvement, the absence of the classical syndrome should not rule out the diagnosis of embolism. Case 1 gave a history of chronic invalidism over many years from right sided pleurisy. The final episode of bilateral "toxic pneumonia" could not be glossed over with dilatory and devotional tactics since the patient could have died. Of course, without necropsy, the diagnosis of pneumonia on the death certificate would have been acceptable to the medical examiner. Case 3 also had several episodes of pleurisy, and embolism was not immediately considered since pleurisy without apparent etiology suggested tuberculosis. When reading of "pneumonia that kills in a few hours," in reports of liberated World War II prisoners who had been subjected to rigid confinement, it is understandable to see how a true diagnosis had been overlooked, but surely in modern hospitals this should not happen.

The well known signs of venous thrombi of the lower extremities cannot always be elicited. Homan's sign of pain on dorsi-flexion of the foot, swelling of the leg, dilated superficial veins, and tenderness over the leg veins may not be demonstrable even if thrombi are present. At this point it may be well to mention that even when the diagnosis of embolism is definite, should one of the extremities be edematous and painful, ligation of the corresponding vein may not prevent recurrence of embolism. A thrombus sufficiently adherent and organized to cause circulatory statis and obstruction would be far less apt to be the source of embolism than an asymptomatic thrombus of the other leg, only partially attached to the side of the vessel. A dangerous thrombus may give little sign of vessel closure and inflammation. In foreboding types of thrombophlebitis, the clot becomes organized and tenaciously adherent to the intima and is therefore less dangerous. Embolism does not occur often in phlegmasia alba dolens.

FIGURE 11

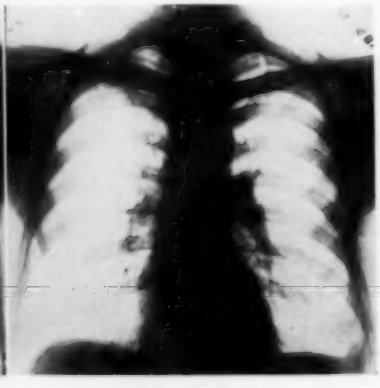

FIGURE 12

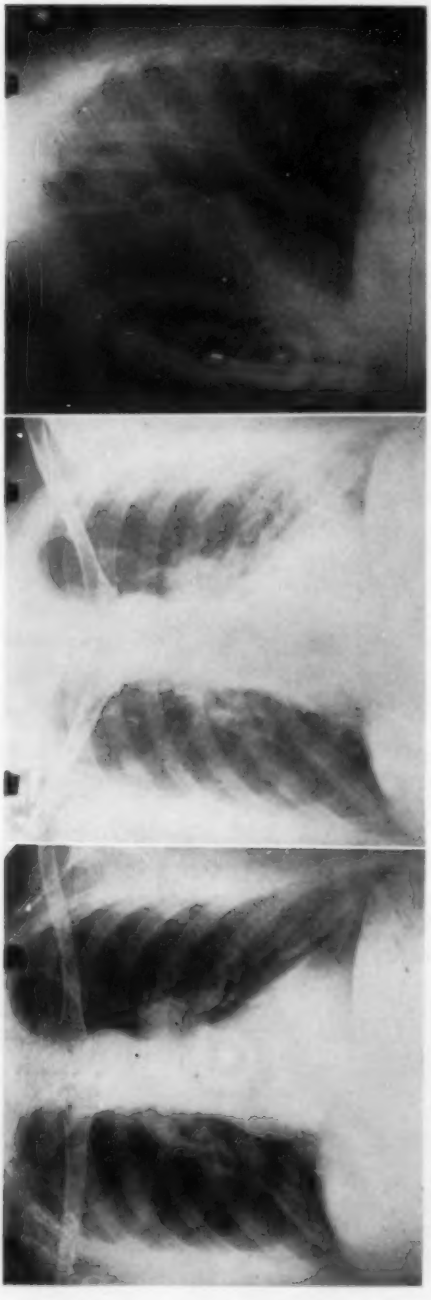

FIGURE 15

FIGURE 14

FIGURE 13

The x-ray film offers little aid in arriving at a definite diagnosis of embolism. Although pulmonary infarcts are usually sharply delimited and wedge shaped at autopsy, the roentgen film will only produce these pathognomonic features if the central ray happens to be made parallel to the side of the infarcts. Fig. 1 through fig. 13 show nothing characteristic of the pulmonary infarcts present, and while this is also true of fig. 14, only its corresponding lateral view (fig. 15) demonstrates the typical wedge shaped shadow of the infarct. When embolism has occurred without infarction, the situation is certainly even more obscure.

SUMMARY

Contrary to what the text books would have us believe, in reviewing cases of patients with embolism, one does not always find the symptoms of chest pain, cough with bloody expectoration, dyspnea, jaundice, and the local lower extremity findings of venous thrombi. Pulmonary embolism takes on many guises, and may masquerade as what appears to be dry or wet pleurisy, bronchitis, bronchopneumonia, lobar pneumonia, pulmonary tuberculosis, cor pulmonale, or unexplained shock. The physician should not treat pulmonary embolism by exorcism. Whether bilateral venous ligation or possibly the administration of heparin or dicumarol is undertaken, the patient will require the most assiduous attention. Long delay has resulted in unnecessary death. We are derelict of duty if the post mortem establishes the true cause of death as a disease that might have been curable.

RESUMEN

Contrariamente a lo que nos pensar los libros de texto, al revisar los casos de enfermos con embolia no siempre encuentra uno los síntomas de dolor torácico, tos con expectoración hemoptoica, disnea, ictericia y los hallazgos locales en las extremidades inferiores de la flebotrombosis. La embolia pulmonar adquiere muchos aspectos y se disfraza con lo que parece ser pleuresía seca o húmeda, bronquitis, bronconeumonía, neumonía lobar, tuberculosis pulmonar, cor pulmonale o choque inexplicado. El médico no debe tratar la embolia pulmonar por exorcismo. Ya sea que se lleve a cabo la ligadura bilateral venosa o el uso de heparina o dicumarol, el enfermo requiere la atención más asídua. El largo retardo ha dado como resultado una muerte innecesaria. Nos sentiremos responsables si el examen postmortem revela la verdadera causa de la muerte si se descubre una enfermedad que podría haber sido curable.

RESUME

Contrairement à ce que les textes voudraient nous faire croire, en faisant la revue des observations de malades atteints d'embolie, on ne trouve pas toujours les symptômes de douleur thoracique, la toux avec expectoration sanglante, la dyspnée, l'ictère et les manifestations de thrombose veineuse localisée aux membres inférieurs.

L'embolie pulmonaire apparait sous des aspects divers et peut prendre le masque d'une pleurésie sèche ou avec épanchement, d'une bronchite, d'une bronchopneumonie, d'une pneumonie lobaire, d'une tuberculose pul-

monaire, d'un coeur pulmonaire ou d'un shock inexpliqué. Le praticien ne devrait pas traiter l'embolie pulmonaire par l'exorcisme. Même si une ligature veineuse bilatérale ou peut-être l'administration d'héparine ou de "dicuoumarol" est entreprise, le malade demande l'attention la plus assidue. Une perte de temps a entrainé un décès qui aurait pu être évité. La responsabilité du médecin est en cause si l'examen *post-mortem* montre que le décès est du à une affection qui aurait pu être curable.

ZUSAMMENFASSUNG

Im Gegensatz zu dem, was uns die Lehrbücher glauben machen, findet man nicht immer bei der Auswertung von Fällen von Kranken mit Embolie die Symptome von Brustschmerz, Husten mit blutigem Auswurf, Kurzatmigkeit, Gelbsucht nebst dem örtlichen Befund einer Venenthrombose an den unteren Extremitäten. Die Lungenembolie nimmt vielerlei Gestalt an und kann erscheinen unter der Maske einer trockenen oder einer feuchten Pleuritis, Bronchitis, Bronchopneumonie, lobärer Pneumonie, Lungentuberkulose, cor pulmonale, oder unerklärter Schock. Der Arzt darf die Lungenembolie nicht durch eine "Geisterbeschwörung" behandeln. Ob man eine bilaterale Venenunterbindung vornimmt oder möglicherweise Heparin oder Dikumarol gibt, der Kranke braucht dann besonders gewissenhafte Aufmerksamkeit. Langes Zögern hat unnötigen Tod zur Folge. Wir machen uns der Pflichtversäumnis schuldig, wenn die Sektion als wahre Todesursache eine Krankheit aufdeckt, die heilbar gewesen wäre.

Embolic Obstruction of Major Pulmonary Arteries Producing Chronic Cor Pulmonale

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and
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The purpose of our presentation is to emphasize this clinical entity which is rare in occurrence, infrequently reported in the literature, and often not diagnosed during life. As massive pulmonary obstruction from an embolus is generally considered as cause for sudden and unexpected death, there is a universal lack of suspicion that a patient may survive and subsequently develop a chronic disease such as cor pulmonale. The signs and symptoms that develop and persist in a period from weeks to years after the initial episode are frequently misinterpreted as due to congenital or rheumatic heart disease, subacute bacterial endocarditis, constrictive pericarditis, periarteritis nodosa, thrombotic thrombocytopenic purpura, or some other obscure entity.

Significant obstruction of the pulmonary artery or its main branches may occur from either thrombosis or embolus. As both conditions produce somewhat similar symptoms and clinical courses, the differentiation may be difficult or impossible during life. When a portion of an embolus lodges in a pulmonary artery and becomes organized with subsequent propagation and formation of thrombi around it, even at necropsy the embolus may not be recognized as such. Thrombosis *in situ* in the pulmonary arterial tree is more apt to occur in patients with parenchymal lung disease and in cases of altered circulation of the pulmonary system due to congenital or acquired heart disease although a number of less frequent causes may also be responsible. The absence of ante-mortem thrombi in the right side of the heart or in the venous system of the abdomen, pelvis, or extremities would be against embolization having contributed to the formation of pulmonary thrombosis. Reports in the literature on pulmonary thrombosis have emphasized these factors as well as etiology, frequency of occurrence, and subsequent development of chronic cor pulmonale.[1,2,3,4]

There are few cases in the American and English literature of chronic cor pulmonale from occlusion of one or both main branches of the pulmonary artery secondary to embolization, whereas there are numerous references to local pulmonary thrombosis *in situ* and of embolization to the tertiary or smaller branches of the pulmonary arteries with pulmonary infarction. Carroll[5] has reported four such cases of embolization to a major pulmonary vessel and included three others from the literature.[6, 7, 8] Petch,[9] Keating,[1] and Hanelin[2] each published an additional case. These

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cases, including an additional one of our own, have certain characteristic signs and symptoms which tend to increase the index of suspicion and make the ante-mortem diagnosis more likely.

A 31-year-old colored male laborer was first admitted to another hospital with thrombophlebitis of the right leg, dyspnea, chest pain, and hemoptysis. His symptoms began six weeks previously with no history of trauma to his leg. Physical examination was not remarkable except for the involved right thigh and leg and moderately enlarged heart. There was no fever. The blood pressure was 136/90 mm. Hg. Pulse rate was 108 per minute. Complete blood count, urinalysis, serology, sedimentation rate, and bleeding and clotting time were all normal. The electrocardiogram revealed sinus tachycardia, right axis deviation, and right ventricular enlargement. The chest x-ray demonstrated cardiac enlargement with marked prominence of the pulmonary artery segment and exaggerated hilar markings believed to be the pulmonary arterial branches. He continued to be dyspneic and expectorate bright red blood and developed pain and tenderness in the left calf. Because of the appearance of right heart failure, he was digitalized and given anticoagulants for the thrombophlebitis and for the suspected pulmonary infarction. With the tentative diagnosis of congenital heart disease, he was transferred to another hospital for further diagnostic studies.

The lungs remained clear and resonant to physical examination. A gallop rhythm was present. The pulmonic second sound was loud and snapping and occasionally some examiners reported mitral systolic and diastolic murmurs. Electrocardiograms and chest films remained essentially unchanged. Cardiac fluoroscopy disclosed marked prominence of the pulmonary artery segment, both right and left ventricular enlargement, but no left auricular enlargement. The significant laboratory data included a sedimentation rate of 36 mm. in one hour, negative sickle cell preparation, occasional one plus albuminuria, casts and red cells in the urine. Cardiac catheterization revealed mean pressures of 6.5 mm. Hg. in the right atrium and 27 mm. Hg. in the right ventricle. The oxygen content of the blood from the right atrium was 15.6 volumes per cent. The catheter could not be introduced into the pulmonary artery. As response to treatment had been fairly satisfactory, he was discharged two months after initial admission with the diagnosis considered at that time as rheumatic heart disease, probably active.

After two months at home he was readmitted to the original hospital with increased dyspnea, pain in the right chest, and hemoptysis. Physical examination disclosed more marked right heart failure with no rales in the lungs. The blood pressure was 130/110 mm. Hg. The spleen was now palpable in addition to the other signs of congestive failure. Nonprotein nitrogen was 22.5 mg. per 100 ml. and the total protein was 6.1 gm. per 100 ml. with albumin-globulin ratio of 3.9/2.2. White blood counts were normal except for two eosinophile counts of 14 per cent and 9 per cent. X-ray films and fluoroscopy of the chest were essentially unchanged with still no left auricular enlargement. The bronchovascular markings were considered more prominent in the

FIGURE 1

FIGURE 2

Figure 1: Chest film demonstrating cardiac enlargement with prominent pulmonary artery segment. An infiltration from pulmonary infarction is present in the right lung.—*Figure 2:* After 10 days, radiolucent areas have appeared in the infiltration indicative of cavitation.

left lung field than in the right, but no definite evidence of pulmonary infarction was demonstrated. A phonocardiogram revealed no murmur. He became febrile and was treated with penicillin and streptomycin although repeated blood cultures were sterile. It was the impression that he had congenital heart disease with subacute bacterial endocarditis. He was transferred to our hospital for further diagnosis and treatment.

Shortly after admission he developed fever, chest pain, hemoptysis, and an infiltration in the right lung field (Fig. 1). In the area of this infiltration, radiolucent areas appeared typical of cavitation (Fig. 2). The electrocardiogram (Fig. 3) revealed right axis deviation, peaked P-waves, right ventricular enlargement, and digitalis effect. The nonprotein nitrogen increased to 77 mg. per 100 ml. and the total protein 7.7 gm. per 100 ml. with albumin-globulin ratio of 2.7/5.0 The red blood count was 5,000,000 per cu. mm. The hemoglobin was 14.2 gm. per 100 ml., and the hematocrit 44 per cent. L. E. cell preparation, skin and muscle biopsy, bone marrow aspiration, and liver biopsy were all normal.

His condition progressively deteriorated. His clinical course was characterized by episodes of dyspnea, orthopnea, cyanosis, chest pain, hemoptysis, fever, and mental confusion. There was increasing congestive failure despite all measures for control. He also had episodes of sudden weakness, prostration, unconsciousness, and shock requiring vaso-pressor drugs. One of these episodes resulted in left hemiplegia. The peripheral edema increased and he progressively became weaker and unresponsive. Death occurred one year after the initial episode of thrombophlebitis.

At autopsy, in addition to the findings of congestive failure, there was almost complete occlusion of the right pulmonary artery by an old thrombus with only a small patent lumen remaining. There was also a thrombus in the left pulmonary artery as well as recent and old thrombi in various stages of organization and recanalization in many of the smaller branches of the arterial system. Several old, healed, as well as recent, pulmonary infarctions were present. The heart was enlarged and weighed 550 gm. with no evidence of valvular or congenital disease. There was right auricular thrombi and an old organized mural thrombus in the right ventricle attached to a scarred and thinned area near the apex. The coronary vessels were normal and patent. There were multiple areas of encephalomalacia in the brain. Exploration of the femoral veins disclosed old organized attached thrombi.

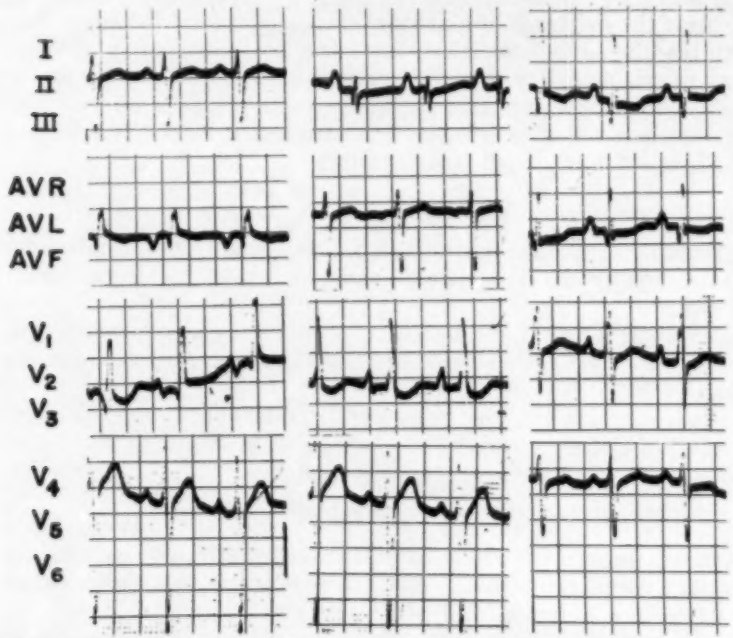

FIGURE 3: Electrocardiogram revealing right axis deviation, peaked P-waves, right ventricular enlargement, and digitalis effect.

Comment

This case illustrates the development of chronic cor pulmonale secondary to embolic obstruction of major pulmonary arteries with the origin of the initial embolus from the recognized thrombophlebitis of the right leg. The origin of the embolus may frequently be obscured by the circumstances of trauma or surgery, not detected clinically, or forgotten by the patient or his physician. Our patient's course was characterized by recurrent acute episodes of dyspnea, hemoptysis, chest pain, fever, syncope, shock, abnormal neurological findings, and mental aberration secondary to repeated occurrences of pulmonary embolism and infarction associated with progressive and intractable right-sided congestive failure. In the reported cases, dyspnea has appeared as the outstanding symptom association with chest pain, fever, and hemoptysis.

Pulmonary embolus without actual pulmonary infarction may produce negative chest findings both clinically and by x-ray inspection. Recent reports,[1,10] however, on pulmonary artery occlusion have emphasized the important x-ray signs of increased radiability and relative absence of the vascular pattern of the involved lung, termination of the major arterial branches at the site of the occlusion, and dilation of the main pulmonary artery proximal to the embolus.

Angiocardiography may demonstrate the absence of filling of the pulmonary vascular tree at the sites of obstruction. Catheterization studies will confirm the presence of hypertension in the pulmonary arterial system and exclude the existence of abnormal shunts of congenital heart disease.

With the diagnosis established, there is a possibility of surgical embolectomy as performed on one of Carroll's patients.[5] Otherwise the treatment is symptomatic, directed at the congestive failure and attempt to prevent recurrence of pulmonary embolism and infarction. This type of management has proved unsatisfactory.

SUMMARY

1. Occasionally patients survive embolism to major pulmonary arteries and subsequently develop chronic cor pulmonale due to occlusion of these vessels.

2. The appearance of right-sided congestive failure in the absence of other obvious causes should suggest this syndrome in the differential diagnosis.

3. Medical treatment has been unsatisfactory and only temporarily palliative at best. A consideration of surgical embolectomy may be entertained once the diagnosis has been established.

RESUMEN

1. Ocasionalmente los enfermos pueden sobrevivir a la embolia de arterias pulmonares principales y más tarde desarrollan corazón pulmonar crónico debido a la oclusión de estos vasos.

2. La aparición de insuficiencia congestiva derecha en ausencia de otras causas evidentes, debe sugerir este síndrome en el diagnóstico diferencial.

3. El tratamiento médico no ha sido satisfactorio y cuando más es paliativo. Una consideración sobre la posibilidad de la embolectomía puede tenerse en cuenta una vez que se ha establecido el diagnóstico.

RESUME

1. Il peut arriver que les malades survivent à l'embolie des grosses artères pulmonaires. Ils évoluent alors vers un coeur pulmonaire chronique consécutif à l'occlusion de ces vaisseaux.

2. L'existence de stase des cavités droites pourrait évoquer ce syndrome en l'absence d'autre cause évidente, lors du diagnostic différentiel.

3. Le traitement médical n'a pas donné de résultats satisfaisants. Le traitement par le repos au lit n'a pu réaliser qu'un palliatif momentané. Une fois que le diagnostic a été établi, l'embolectomie chirurgicale pourrait être envisagée.

ZUSAMMENFASSUNG

1. Gelegentlich überleben Kranke die Embolie von grösseren Lungenarterien und ziehen sich ein chronisches cor pulmonale zu als Folge des Verschlusses dieser Gefässe.

2. Das Auftreten von rechtsseitigem Herzversagen durch Stauung bei Fehlen anderer augenfälliger Ursachen muss dieses Syndrom in der Differenzialdiagnose nahelegen.

3. Interne Behandlung ist unbefriedigend gewesen und bestenfalls zeitweilig palliativ. Eine Erwägung hinsichtlich chirurgischer Embolektomie kann angestellet werden, sobald die Diagnose feststeht.

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Editorial

Need for Long-Acting Tuberculin Test

Of the 100,00 to 200,000 Americans who will die from tuberculosis during the next 10 years, virtually all will have developed tuberculin sensitivity long before the time of death. Unsought for in many and therefore silent, this warning will have passed unrecognized during the early, most treatable period of the disease. From a practical point of view, human tuberculosis is contracted through infection from other humans in whom tuberculin sensitivity has already developed. The reservoir of infection thus constitutes a certain percentage of our tuberculin sensitive population. Only when this reservoir is eliminated will tuberculosis have been controlled. Tests for tuberculin sensitivity may prove to be of comparable significance to drugs, surgery, and chest x-ray films.

The *mass* chest x-ray survey, admittedly of good propaganda value, is a poor approach to tuberculosis control. Positive radiographic findings usually lag well behind the onset of disease. The colossal inefficiency of *mass* survey technics is comparable to that of shooting ducks by blindly firing a machine gun in the general direction of the flock. Although certain bullets will find a target, many will be expended needlessly. The wise hunter aims at his quarry. Tuberculin or similar testing represents the "aim" of the analogy. In the search for tuberculosis, why should 10 be x-rayed when only two are tuberculin sensitive and therefore disease suspects? Since mass tuberculin testing is not yet extensively practical, it would be wise to plan chest surveys in a more deliberate, less random fashion, working through clinics, low-income areas, and susceptible population groups, rather than on Main Street or in the ball park. While a mass chest x-ray survey in the United States might reveal a 1 per cent incidence of significant pulmonary tuberculosis, such a study on the Alaskan native population would be 25 times as effective! Similar reasoning should be applied to the use of large scale tuberculin testing. Infant and child health programs probably offer the best approach since here will be found the highest return of early, treatable disease although countywide testing of people of all ages has been found of great value in locating the seed beds of tuberculosis among older persons.

The tuberculin test and the chest x-ray film are not competitive control measures; they are complementary. By means of the tuberculin test, those individuals can be discovered who harbor the tubercle bacillus. Here, repeated, routine chest roentgenography is indispensable in diagnostic follow-up and when treatment is instituted. In the interest of logical tuberculosis control planning, it is here advocated that more funds be devoted to the exploitation and improvement of tuberculin sensitivity detection. It is suggested that the following proposed approach deserves strong financial support.

If warranted by available knowledge, *a major investigative effort should*

be directed toward the development of a "depot" or long-acting test for tuberculin sensitivity. Currently, the tuberculin test reveals only those individuals who have been infected with tuberculosis at least four weeks prior to the time of testing. Hypothetically, children now being tested for tuberculosis can be infected immediately before or soon after the test is performed. Ironically, in such cases failure to disclose that the disease had been contracted would give a false sense of security. At present, an adequate control program would consist of repeated tuberculin testing on an annual basis, (or until sensitivity is demonstrated which involves a large volume of work). An antigen should be sought which, placed in the body, would be quiescent but potent. Upon the subsequent appearance of tuberculin sensitivity, the antigen should produce a clinically recognizable response, thus drawing attention at the earliest possible moment to the onset of infection. Depot-type drugs are in widespread use today. Certain of these involve proteins. Lovelace has shown that antigenic substances used in the treatment of hypersensitivity states can be administered in such a manner as to remain effective for as long as a month. Ideally, a "tuberculin test" should be developed with life-time potency. One test would therefore serve to call attention to the onset of tuberculosis at any subsequent time in the individual's life. Of necessity, the patient would have to be instructed in the recognition of a positive reaction. Ideals in medicine are rarely achieved, however, and such a solution may not prove possible. Nevertheless, extension of the potency period of the tuberculin test to one month, six months, a year, or more, would be of great value.*

Charles T. Dotter, M.D., F.C.C.P.

*The value of such a test is more apparent than a possible method. Conceivably, there might be worked out a means of incorporating an antigen into a tooth filling, a root canal, or a dental cap. Thus, by gradual wear and tear, sufficient amounts of the antigen might be liberated as to make possible a positive patch test on the buccal mucosa when tuberculin sensitivity subsequently developed. Intra-osseous, intramuscular, and subdermal sites for antigen placement could be explored.

The President's Page

Last month I called your attention to the interesting and informative reports of our Councils and Committees published in recent issues of *Diseases of the Chest*. In this issue you will find equally informative reports by the Councils on Postgraduate Medical Education and International Affairs, as well as the reports of the Board of Examiners and the Committees on Audiovisual Aids, Essay Award and Membership.

You will be interested, I believe, in the progress of our Committee on Cardiovascular Disease. As you may know, this Committee, under the Chairmanship of Dr. George R. Herrmann of Galveston, Texas, is composed of the following sections and their chairmen:

Clinical Cardiovascular Disease	Arthur M. Master, New York, N. Y.
Pediatric Cardiology	Benjamin M. Gasul, Chicago, Illinois
Cardiovascular Surgery	Charles P. Bailey, Philadelphia, Pa.
Therapy	John J. Sampson, San Francisco, Calif.
Cardiovascular Physiology	Aldo A. Luisada, Chicago, Illinois
Roentgenology	Israel Steinberg, New York, N. Y.
Electrocardiography	Irving Mack, Chicago, Illinois
Rehabilitation	Ray W. Kissane, Columbus, Ohio

Dr. Master's Section on Clinical Cardiovascular Disease will continue its study, begun last year, on blood pressure in the older population and will devote this year to obtaining statistics on blood pressure readings in people 90 years of age or older. The Section on Cardiovascular Surgery, of which Dr. Charles P. Bailey is Chairman, is now compiling statistics on coarctation of the aorta. A report on this project, similar to the one on "The Surgery of Patent Ductus Arteriosus" published in the January issue of *Diseases of the Chest*, will be presented at the Annual Meeting of the College. Some sixty outstanding cardiovascular surgeons throughout the world are cooperating with this section in compiling data for the study.

The Section on Cardiovascular Physiology, under the Chairmanship of Dr. Aldo A. Luisada, is promoting a competition for an essay on "Acute Pulmonary Edema—Experimental or Clinical Studies." The closing date for the entries is May 1, 1956 and a prize of $500 will be awarded to the winner.

The Section on Therapy, headed by Dr. John J. Sampson, will undertake an evaluation of the current methods of treatment in cardiovascular disease and will publish the information compiled. The other sections of the Committee on Cardiovascular Disease are now selecting their projects and will begin their work in the near future.

An unusually large number of undergraduate medical students are registering for this year's essay contest. The deadline for entries is April 15, 1956 and if you know of some bright medical student who should be encouraged to compete for the several prizes and certificates of merit, urge him to apply at once to the Council on Undergraduate Medical Education for further information.

All of our councils and committees are functioning and it is planned to have their reports presented at our 22nd Annual Meeting, to be held in Chicago, Illinois, June 7-10, 1956. I hope that you are planning to attend this meeting and I would suggest that you apply early for hotel accommodations. You will find a hotel reservation form in this issue of the journal.

James H. Stygall

22nd ANNUAL MEETING

The 22nd Annual Meeting of the American College of Chest Physicians will be held at the Hotel Sherman, Chicago, Illinois, June 7-10, 1956. The Committee on Scientific Program, under the chairmanship of Dr. William A. Hudson, is organizing an outstanding program.

On Thursday, June 7, the annual meetings of College councils and committees, as well as the Board of Regents and Board of Governors, will be held. The regular scientific program will open on Thursday evening with the presentation of the first Louis Mark Memorial Lecture, to be followed by an interesting symposium on carcinoma. The scientific program will continue through Friday, Saturday and Sunday, June 8-10, including round table luncheons, fireside conferences, motion pictures and panel discussions. The annual convocation and Presidents' Banquet will be held on Saturday evening, June 9.

A number of seminars will be presented as refresher courses on Wednesday, June 6, one day prior to the opening of the annual meeting. Registration for these refresher courses will be limited and applications will be accepted in the order in which they are received.

Hotel reservations may be obtained by contacting the Hotel Sherman, Chicago 1, Illinois, and it is advisable that accommodations be reserved early. Please refer to page xii of this issue for a convenient reservation form and send it to the Hotel Sherman today.

COLLEGE INTERIM SESSION

The Interim Session of the College was held at the Sheraton Plaza Hotel, Boston, Massachusetts, on Monday, November 28, 1955. More than 200 physicians registered for the meeting and attended the interesting scientific program organized by the New England States Chapter of the College. The round table luncheons were filled to capacity and more than 150 physicians attended the Fireside Conferences which were held on Sunday evening, following a dinner sponsored by the chapter. Dr. John B. Andosca, President of the New England States Chapter, presided at the dinner and Dr. Howard F. Root, College Governor for Massachusetts, introduced Dr. James H. Stygall, President of the College, who spoke briefly on College activities. Dr. Richard H. Overholt, who served as chairman of the scientific program committee for the meeting, was introduced and he and his committee members were congratulated for the splendid program they had arranged. The chairmen and members of all the local committees were given a vote of appreciation by the Board of Regents for the organization of an outstanding meeting.

The Board of Regents and Board of Governors of the College held their semi-annual meetings in Boston on Sunday, November 27, and a report of these meetings follows.

Semi-Annual Meeting

BOARD OF REGENTS AND BOARD OF GOVERNORS

The Semi-Annual Meetings of the Board of Regents and the Board of Governors of the American College of Chest Physicians were held at the Sheraton Plaza Hotel, Boston, Massachusetts, on Sunday, November 27, 1955. Dr. David H. Waterman, Chairman of the Board of Governors, presided at the Joint Meeting, and Dr. John F. Briggs, Chairman, presided at the meeting of the Board of Regents. The following Regents, Governors, council and committee members, and guests were present:

James H. Stygall, Indianapolis, Indiana, President
John F. Briggs, St. Paul, Minnesota, Chairman, Board of Regents
David H. Waterman, Knoxville, Tennessee, Chairman, Board of Governors
Robert J. Anderson, Washington, D. C.
John B. Andosca, Boston, Massachusetts
Albert H. Andrews, Chicago, Illinois
Gerald Beatty, Wilmington, Delaware
B. Guy Begin, Montreal, Quebec
Otto L. Bettag, Chicago, Illinois
Francis D. T. Bowen, Hartford, Connecticut
Otto C. Brantigan, Baltimore, Maryland

J. Maxwell Chamberlain, New York City
William P. Chester, Detroit, Michigan
Ross K. Childerhose, Harrisburg, Pennsylvania
Dean B. Cole, Richmond, Virginia
James P. Cooney, Washington, D. C.
Simon Dack, New York City
Edgar W. Davis, Washington, D. C.
Hugo T. Ewart, Hamilton, Ontario
Russell H. Frost, Oak Terrace, Minnesota
Carl H. Gellenthien, Valmora, New Mexico
Alfred Goldman, St. Louis, Missouri
Burgess L. Gordon, Philadelphia, Pennsylvania
Edward A. Greco, Portland, Maine
Alvis E. Greer, Houston, Texas
J. E. J. Harris, Albuquerque, New Mexico
Juan R. Herradora, Jersey City, New Jersey
William A. Hudson, Detroit, Michigan
Chevalier, J. Jackson, Philadelphia, Pennsylvania
Francis J. Kasheta, Glencliff, New Hampshire
Roy G. Klepser, Washington, D. C.
Edwin R. Levine, Chicago, Illinois
Donald R. McKay, Buffalo, New York
Frank A. Merlino, Providence, Rhode Island
Herman J. Moersch, Rochester, Minnesota
Jay Arthur Myers, Minneapolis, Minnesota
H. Allan Novack, Boston, Massachusetts
Richard H. Overholt, Boston, Massachusetts
J. Winthrop Peabody Sr., Washington, D. C.
Charles K. Petter, Waukegan, Illinois
Joseph C. Placak Sr., Cleveland, Ohio
Wilhelm Raab, Burlington, Vermont
Howard F. Root, Boston, Massachusetts
Frank G. Seldon, Manchester, New Hampshire
P. J. Sparer, Memphis, Tennessee
Harold G. Trimble, Oakland, California
H. S. Van Ordstrand, Cleveland, Ohio
Buford H. Wardrip, San Jose, California
Irving Willner, Newark, New Jersey
Murray Kornfeld, Chicago, Illinois, Executive Director
Harriet L. Kruse, Chicago, Illinois, Executive Assistant

Following roll call and signing of the College Roster, Dr. Overholt, chairman of the committee on general arrangements for the Interim Session of the College, welcomed the members to Boston and related briefly the program which had been arranged by the New England States Chapter of the College.

The following reports were presented:

Council on Postgraduate Medical Education

Four postgraduate courses on diseases of the chest were sponsored by your Council on Postgraduate Medical Education this fall. A postgraduate course for general practitioners was arranged by Dr. Edward Lebovitz in Pittsburgh and was presented in five Sunday morning sessions during the month of October. This postgraduate course was attended by 49 physicians and favorable comments were received. Dr. Lebovitz is to be congratulated on his successful efforts.

The Tenth Annual Postgraduate Course on Diseases of the Chest was presented in Chicago, October 3 through 7. This was one of the finest courses presented in Chicago and we have received many complimentary letters about it. The course was attended by 59 physicians. Dr. Edwin R. Levine and his committee can be proud of their splendid work during the past ten years in furthering postgraduate medical education in chest diseases.

New York City was host to its Eighth Annual Postgraduate Course on Diseases of the Chest during the week of November 14-18. The registration for the course is 114 physicians which surpasses that of last year's course. Dr. Edgar Mayer and Dr. Alfred Dooneief, the co-chairmen, and their committee members, have done an excellent job, as usual, in the organization of this postgraduate course.

The final postgraduate course for 1955 is being presented in Los Angeles, December 5 through 10. Dr. Alfred Goldman and Dr. Seymour M. Farber, Co-Chairmen, with the assistance of their committee, have organized an outstanding course. The registration for the course is 137, including twenty scholarships awarded by the Los Angeles Tuberculosis and Health Association, and four awarded by the Long Beach Tuberculosis and Health Association. Other cooperating agencies are the Los Angeles County Heart Association and the Section on Diseases of the Chest of the Los Angeles County Medical Association.

The first postgraduate course to be sponsored by the College in 1956 will take place in Philadelphia, March 19-23. These dates were recently announced by Dr. Chevalier L. Jackson and Dr. Katharine Boucot, Co-Chairmen of the course, and it will be the Ninth Annual Postgraduate Course on Diseases of the Chest to be held in Philadelphia. We know that Drs. Jackson and Boucot and their committee will organize the usual splendid program and we anticipate a very successful course for Philadelphia.

J. Winthrop Peabody, Sr., Chairman

Board of Examiners

Sixty-six candidates took the oral and written examinations for Fellowship in the College in Atlantic City on June 2, 1955, and one candidate was re-examined orally. Of the 66 who were examined, four were required to retake the oral portion of the examination. One of these has now been re-examined and has passed.

It was reported to this Board in June, 1955 that the Board of Examiners had met preceding the meeting in Atlantic City and had discussed changing the type of examination for advancement to Fellowship. The Board of Examiners felt that a multiple-choice type of examination should be given for the written portion.

Such an examination is being developed. It has been worked out that there will be 15 questions of a general nature, which all candidates must attempt to answer. The candidates will then select the balance of their written examination by one of two routes: That of pulmonary disease or of cardiovascular disease. They will then be given a list of questions in either of these fields to consist of 50 multiple-choice questions, of which they should answer 35. This examination should not take more than two hours, but three hours will be allotted—from 9:00 a.m. to 12:00 noon.

Harold G. Trimble, Chairman

Committee on Membership

At the time of the Annual Meeting in June 1955, the membership of the College was 5204. Between March 15 and September 15, 1955, 289 applications were received and presented to the Board of Regents. Of these applications, 135 were for Fellowship, 80 for Associate Fellowship, 42 for Associate Membership, 31 for Advancement to Fellowship and 1 for Advancement to Associate Fellowship. Of this group, 203 were from physicians in the United States and Canada, and 86 were filed by physicians in other countries.

Of the total of 289 applications presented to the Board of Regents, 2 were definitely rejected and 10 are being held for further investigation. Therefore, 245 new members were admitted to the College since the Annual Meeting in June 1955, bringing the total College membership to 5449, which represents an increase of 410 new members admitted during 1955.

We now have 43 applications which have been filed between September 15 and November 7. This group will be presented to the Board of Regents at our Annual Meeting in June 1956.

Chevalier L. Jackson, Chairman

Committee on College Essay

Posters concerning the Prize Essay Contest of the College, such as the one you have seen in your brochure, have been mailed by the Executive Offices of the College, together with appropriate letters, to the following: Approximately 250 were sent to deans of medical schools throughout the world; 68 went to Chapter Presidents of the Student American Medical Association and

to medical fraternities in the United States and Canada; 125 posters were mailed to Regents and Governors of the College in countries throughout the world; and posters were also mailed to members of the Council and the Committee on Undergraduate Medical Education of the College. They were asked to cooperate with the Council on Undergraduate Medical Education of the American College of Chest Physicians by posting the announcement of the 1956 Essay Contest on the bulletin boards of their schools.

A number of letters have been received from deans and students at medical schools in the United States, Canada, Honduras, Ireland, Peru, England, Scotland, Germany and Australia, expressing interest in the Contest and assuring their cooperation in giving it the utmost publicity at their schools.

News releases concerning the 1956 Essay Contest of the College were mailed to medical journals throughout the world with the request that they publish the announcement in their respective journals.

Requests for information and applications have been received from a number of medical students. One manuscript submitted for the 1955 Contest by a medical student in India was received too late and has been held over for the coming competition.

Joseph S. Hiatt, Chairman

Committee on Audiovisual Aids

The Committee on Audiovisual Aids was formed February 8, 1955, for the purpose of collecting a slide library for the teaching of diseases of the chest to undergraduate medical students.

The Committee has worked very closely since the beginning with the Council on Undergraduate Medical Education through its chairman, Dr. E. W. Hayes, who has been most helpful in devoting time and thought and sharing from his experience and thinking in the field of teaching of chest diseases. Dr. H. G. Trimble has also contributed very helpfully to the work of the Committee.

A collection of over eighty 35 mm. slides on pulmonary tuberculosis has been assembled. The medium of 35 mm. lantern slides was chosen, because the original collection can be very easily supplemented; new and better slides can be inserted; and less desirable or out-dated slides can be replaced. When a little more complete, the collection will be tried on a medical school class in diseases of the chest.

The activities of this committee will be continued under Dr. Theodore Noehren, the new Chairman of the Council on Undergraduate Medical Education. Dr. Hayes will continue his services on the Council as Vice-Chairman.

The Committee expresses herewith its thanks to all those who are taking such an interest and are being so helpful in advancing this work.

Robert B. Stone, Chairman

Council on International Affairs

Following a conference held in Milwaukee and a subsequent conference with the Executive Committee in Germany, it was agreed that the following themes would be presented at the Fourth International Congress on Diseases of the Chest to be held in Cologne, Germany, August 19-23, 1956:

Coronary Diseases
Industrial Diseases of the Chest
Tuberculosis
Pulmonary Function
Cardiac Function
Tumors of the Mediastinum

In addition to formal presentations, a special panel of experts will be selected to discuss each of these subjects and there will be free discussion from the floor. At the end of each daily session at 5:00 p.m., Fireside Conferences will take place in the Ratskeller of the Gurzenich, where the Congress will be held. Special provisions will be made for the presentation of papers dealing with topics unrelated to the main themes. Present plans are to hold the scientific sessions in two assembly halls equipped for simultaneous translation by the use of head phones. Motion pictures will be shown throughout each day of the Congress.

Up to the present time, requests have been received from 124 physicians for places on the scientific program, representing 34 countries and territories throughout the world. These requests cover a variety of subjects dealing with many aspects of diseases of the chest. The Council on International Affairs will study these requests and those which can be fitted into the scientific program will be accepted and the physicians notified to prepare their manuscripts. In order to assure adequate translation and proper presentation of the subject matter, it is essential that all manuscripts be submitted ninety days prior to the opening of the Conference.

Andrew L. Banyai, Chairman

Mr. Murray Kornfeld, Executive Director of the College, discussed the arrangements being made for the Congress, as well as the planned post-convention tour, and called attention to the article concerning the Congress which appeared in the December, 1955 issue of *Diseases of the Chest*. Dr. Jackson extended an invitation to the members of the College to attend the Congress of the Internation Broncho-esophagological Society to be held in Vienna, Austria, August 31—September 2, 1956.

Dr. Robert J. Anderson presented the report of the Council on Public Health, referring mainly to their published report "Participation of Physicians in Private Practice in Basic Tuberculosis Control Procedures" which appeared in the November, 1955 issue of *Diseases of the Chest*.

The report of the Committee on College Chapters was presented by Dr. Greer, and accepted with a vote of appreciation. (This report was published in the January, 1956 issue of *Diseases of the Chest*).

Dr. J. Arthur Myers, Editor of the College journal, *Diseases of the Chest*, reported that effective January 1, 1956, Section XV of *Excerpta Medica*, formerly known under the title of "Tuberculosis and Pulmonary Diseases," will be re-named "Chest Diseases." This revised edition of *Excerpta Medica* will be sponsored by the American College of Chest Physicians. The editorial board has been revised to include an additional number of Fellows of the American College of Chest Physicians in countries throughout the world. Mr. Murray Kornfeld has had several conferences with Mr. P. A. Warren, the business manager of *Excerpta Medica*, and all of the arrangements in connection with the publication of the revised issue have been completed. The College will co-operate with the publishers of *Excerpta Medica* in stimulating interest among the members of the College and other physicians in this publication and it is hoped that a large number of our members will subscribe to this excellent abstract service.

Dr. Gordon reported that as chairman of the editorial committee for the proposed book on *Clinical Cardiopulmonary Physiology*, plans were progressing in the organization of the chapters and the selection of authors, and that arrangements have been completed for the publishing of the book. It was reported that the book *Nontuberculous Diseases of the Chest*, recently published by the College under the chairmanship of Dr. Andrew L. Banyai, Milwaukee, had been very well received. The book on *Problems in Thoracic Surgery*, under the chairmanship of Dr. Alfred Goldman, Beverly Hills, California, will be ready for publication within a short time, as most of the chapters have been completed. Dr. Coleman B. Rabin of New York City has announced that the book on *Roentgenology of the Chest* is well under way and that a number of chapters have already been submitted. Negotiations have been completed with the publishers relative to the printing and distribution of these new College books.

Dr. Hudson, immediate Past President of the College, who is serving as chairman of the Committee on Scientific Program for the 22nd Annual Meeting to be held at the Hotel Sherman, Chicago, Illinois, June 7-10, 1956, reported that he and his committee members were giving their attention to the organization of an outstanding program. A brief outline of the program appeared in the January, 1956 issue of the journal.

Adjournment.

COMMITTEE ON NOMINATIONS

Elections for offices expiring in June, 1956 will be held at the Hotel Sherman, Chicago, on June 9. Recommendations for elective offices may be addressed to the chairman of the Committee on Nominations, Dr. Carl H. Gellenthien, Valmora Sanatorium, Valmora, New Mexico. Other members of the committee are Dr. Buford H. Wardrip, San Jose, California and Dr. Benjamin L. Brock, Orlando, Florida.

9th ANNUAL PHILADELPHIA POSTGRADUATE COURSE

The Ninth Annual Postgraduate Course on Diseases of the Chest, sponsored by the Council on Postgraduate Medical Education of the College, will be held at the Bellevue-Stratford Hotel, Philadelphia, Pennsylvania, March 19 through 23, 1956. Drs. Chevalier L. Jackson and Katharine R. Boucot are co-chairmen for the course and with the cooperation of their committee members, have organized an excellent program. Tuition fee for the postgraduate course is $75.00, including round table luncheon discussions. Physicians interested in registering for the course may apply to the Executive Offices of the American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois. As registration for the course is limited, applications will be accepted in the order received.

College Chapter News

PUERTO RICO CHAPTER

The Puerto Rico Chapter held its annual meeting on December 8 at the Club de la Prensa, San Juan. The following officers were elected:

President:	Hector Martinez Villafane, Santurce
Vice President:	Juan Ramon Marchand, Santurce
Secretary-Treasurer:	Francisco Carlos Porrata, Ponce

In addition to the new officers, the following were elected to serve on the Membership Committee: Felix M. Reyes, San Juan; Edmundo Figueras, Santurce; Jose Pico, Santurce; Juan J. de Lara-Garcia, Ponce. At the close of the meeting, the chapter members attended a dinner at El Patio Espanol.

NEW JERSEY CHAPTER

A meeting of the New Jersey Chapter will be held on February 28 at the B. S. Pollak Hospital, Jersey City. Dr. Richard H. Overholt, Director of the Overholt Clinic, Boston, Massachusetts, has been chosen to present the Second Selman Waksman Lecture. Dr. Overholt will speak on "Carcinoma of the Lung: Direct Approach to Shadow and Substance."

HONG KONG AND CHINA CHAPTER

The Hong Kong and China Chapter met at the Hong Kong Sanatorium and Hospital on December 12. Following a dinner for members and their guests, a symposium on "The Modern Treatment of Pulmonary Tuberculosis" was presented. The panel was composed of Sister Mary Aquinas, Kenneth Hui, and Li Shu-Pui of Hong Kong. An open discussion followed. At the business meeting of the chapter, the following officers were elected:

President:	Kenneth L. Hui, Hong Kong
Vice President:	Sister Mary Aquinas, Hong Kong
Secretary-Treasurer:	Stephen D. Sturton, Hong Kong (re-elected)

The meeting concluded with a convocation at which Dr. Li Shu-Fan, Governor of the College for Hong Kong, presided. Fellowship certificates were presented to new members and Dr. Kenneth L. Hui presented a certificate of merit to Dr. Li Shu-Fan in recognition of his services to the College.

MICHIGAN CHAPTER

The Michigan Chapter of the College will present a scientific program on Wednesday, February 8, 1956 at the William H. Maybury Sanatorium, Northville, Michigan, at 8:00 P.M. All physicians are cordially invited to attend. An election of officers will be held at this time.

NORTH INDIA CHAPTER

The North India Chapter met on November 12 at the Victoria Jubilee Hospital, Amritsar. Dr. K. L. Wig, Governor of the College for North India, presided at the scientific session in which papers were presented by the following: R. P. Malhotra, Y. S. Bawa, and S. S. Manchanda.

College News Notes

Dr. Donald L. Paulson, Dallas, Texas, and **Dr. Hawley H. Seiler,** Tampa, Florida, were recently elected President and Secretary-Treasurer respectively of the Southern Thoracic Surgical Association at the annual meeting held recently in White Sulphur Springs, West Virginia.

Dr. Irving Willner, Newark, New Jersey, was appointed Consultant in Tuberculosis at the Hospital of St. Barnabas and the Women and Children's Hospital. Dr. Willner also lectured before physicians of the Veterans Administration Hospital, Newark, on "Prophylaxis versus Chemotherapy in the Eradication of Tuberculosis."

Dr. Jay Arthur Myers, Minneapolis, Minnesota, spoke before the Alameda Contra Costa Medical Society and the Alameda County Tuberculosis and Health Association on January 16, 1956 in Oakland, California. On the morning of January 16, he participated in a workshop devoted to a review of the methods of tuberculosis control in regard to the nursing staff of hospitals. In the afternoon, at the invitation of the California State Department of Public Health, a select group of approximately 150 members of the State Health Department staff, the University of California School of Public Health, local health officers and their associates, some social workers, nursing supervisors and interested physicians, met to discuss with Dr. Myers the general problem of tuberculosis control from the standpoint of State and County Health Departments.

Following a dinner with the officers of the Alameda Contra Costa Medical Society, Dr. Myers presented an address on "Modern Aspects of Diseases of the Chest."

ANNOUNCEMENT

The French National Committee Against Tuberculosis, in cooperation with the International Union Against Tuberculosis and the Antoine Beclere Center of International Relations in Medical Radiology, will sponsor the Second International Congress of Medical Radiophotography to be held in Paris, France, April 4-7, 1956. Professor Manoel de Abreu is Honorary President of the Congress, Prof. Maurice Bariety will serve as President, and the Secretaries General are: Professor Pierre Desgrez, Dr. William Gellner, and Dr. Andre Meyer.

Information concerning registration, hotels, procedure, social functions, etc., as well as a copy of the preliminary program, may be obtained by writing to the Secretariat, Second International Congress of Medical Radiophotography, 66, Boulevard St-Michel, Paris 6, France.

BOOK REVIEW

"LUNG CANCER"

by Seymour M. Farber, Charles C Thomas Publisher, Springfield, Illinois, 1954.

This monograph is a welcome addition to the medical literature. It offers a remarkably clear illucidation of its subject. The comprehensive presentation of the histopathologic aspects of lung cancer facilitates the diagnostic approach to this condition. Controversial and unsettled questions are discussed by the author in an unbiased manner and with the modesty of a great scientist. Dr. Farber's pioneering work in the cytologic diagnosis of carcinoma of the lung endows his writing with competence and reliability. His vast experience in chest diseases is reflected in the chapters which deal with the diagnosis and treatment of this disease. In spite of its conciseness, this text should serve as a useful, practicing guide for the practicing physician as well as for students of medicine. The format of the book is excellent. The quality of roentgenographic illustrations is highly satisfactory. The up-to-date bibliography and the index greatly enhance the value of this volume.

Andrew L. Banyai, M.D.

Obituary

HARRY MANDELBAUM

1895-1955

Dr. Harry Mandelbaum, a Fellow of the American College of Chest Physicians of Brooklyn, New York, passed away on May 27, 1955. Dr. Mandelbaum was a graduate of the Long Island College Hospital of Medicine.

Dr. Mandelbaum was eminently known in the field of cardiology, and in 1953, he co-authored a book entitled *Ballistocardiography* with Drs. William Dock and R. A. Mandelbaum. In 1954, he visited Israel and lectured at the Hebrew University. He was active in various medical societies, most especially in the Kings County Medical Society in which he served as a member of the Board of Trustees, Treasurer, and as alternate delegate to the New York State Medical Society. His memberships included the American College of Cardiology, American Geriatric Society, World Medical Association, Brooklyn Society of Internal Medicine, New York Cardiological Society, and the American College of Physicians. Until his death, he was Clinical Professor of Medicine at the State University of New York, College of Medicine.

Dr. Mandelbaum is survived by his wife Rose.

Foster Murray, M.D.
Governor

MEDICAL SERVICE BUREAU
POSITIONS AVAILABLE

Full time physicians wanted for new 440-bed tuberculosis division of large general hospital in east; available immediately; associated with two medical schools for teaching purposes; opportunity for research; complete surgical and pathological facilities; salary governed by background and experience. Please address all inquiries to Box 286A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Assistant Medical Director wanted, 100 bed tuberculosis hospital, North American graduate; salary $8,500, complete maintenance. Apply: Medical Director & Superintendent, District Five Tuberculosis Hospital, London, Kentucky, or State Tuberculosis Hospital Commission, New State Office Building, Frankfort, Kentucky.

Medical Director wanted, North American graduate, five years tuberculosis experience. Relatively new 100 bed tuberculosis hospital. Salary $10,000, complete maintenance. Apply: State Tuberculosis Hospital Commission, New State Office Building, Frankfort, Kentucky.

Physicians specializing in tuberculosis and chest diseases wanted for 600 bed hospital, located 30 miles from Springfield, Missouri. Developing pediatric department, in-service and affiliation program. Merit system benefits. Full maintenance and laundry minimum rate. Following positions are open: Physician I (tuberculosis) $6,000—$8,000; Physician II (tuberculosis) $8,000—$11,000; Physician III (tuberculosis) $10,000—$13,000. Write: Medical Director Missouri State Sanatorium, Mt. Vernon, Missouri.

The Health Department, City of Ottawa (Canada) requires physician as Director of Tuberculosis Prevention and Director, May Court Chest Clinic. Clinic functions in close cooperation with Royal Ottawa Sanatorium and Ottawa Anti-tuberculosis Association. Registry and Clinic housed in modern, downtown building with adequate staff. Salary approximately $6,700 per annum, possibly more if board certified. Apply to Secretary, Board of Health, Room 108, 48 Rideau Street, Ottawa, Ontario, Canada.

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J. Lloyd Eaton, M.D., Oakland
Gerald L. Crenshaw, M.D., Oakland
Glenroy N. Pierce, M.D., San Francisco
James Kieran, M.D., Oakland
Robert Stone, M.D., Oakland
William B. Leftwich, M.D., Oakland

Medical Service Bureau (continued)

Immediate opening for staff and resident physicians in tuberculosis hospital. Service includes a great deal of internal medicine and chest surgery. Approved pulmonary disease residency. Excellent salary, plus maintenance if desired. Eligibility for state license required. Write: Superintendent, Sunnyside Sanatorium, Indianapolis 26, Indiana.

Phthisiologist wanted—for Guam; to team with qualified thoracic surgeon in new 160-bed tuberculosis hospital. Salary $11,200 per annum; two year contract; transportation self and family both ways; housing at government rental; sick and annual leave. Requirements: U. S. citizenship, at least two years specialized training in tuberculosis and diseases of the chest plus two years experience, or equivalent. Write: Director, Medical Services, Government of Guam, Agana, Guam.

Tuberculosis physicians wanted to staff new 200-bed, air-conditioned sanatorium, opening July 1, 1956. Adjacent Medical College of Virginia and its hospital; complete facilities available for chest surgery, surgical and other consultation; out-patient clinics; occupational therapy; rehabilitation; opportunities for teaching and research; eligibility for licensure in Virginia required; all positions covered by social security, state retirement, vacation and sick leave:

Medical Director: position open now. Salary range $12,000 to $13,128; five or more years clinical experience in tuberculosis, four of which served in approved sanatorium, and one year in a senior grade; one or more additional years satisfactory experience may be substituted for sanatorium service; board certification internal medicine desirable.

Physician B (3): Salary range, $9,600 to $11,472; two years experience in approved tuberculosis sanatorium or two years in clinic or office practice under supervision of competent chest specialist; two years general practice may be substituted for one year sanatorium or non-sanatorium specialized chest disease experience.

Physician A (1): Salary range $8,400 to $9,168.

Apply to: Mack I. Shanholtz, M.D., State Health Commissioner, Department of Health, Richmond 19, Virginia.

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For the treatment of tuberculosis and diseases of the chest, situated near Colorado Springs in the heart of the Rockies. Ideal year-round climate. Individual apartments, with or without baths. Rates on request.

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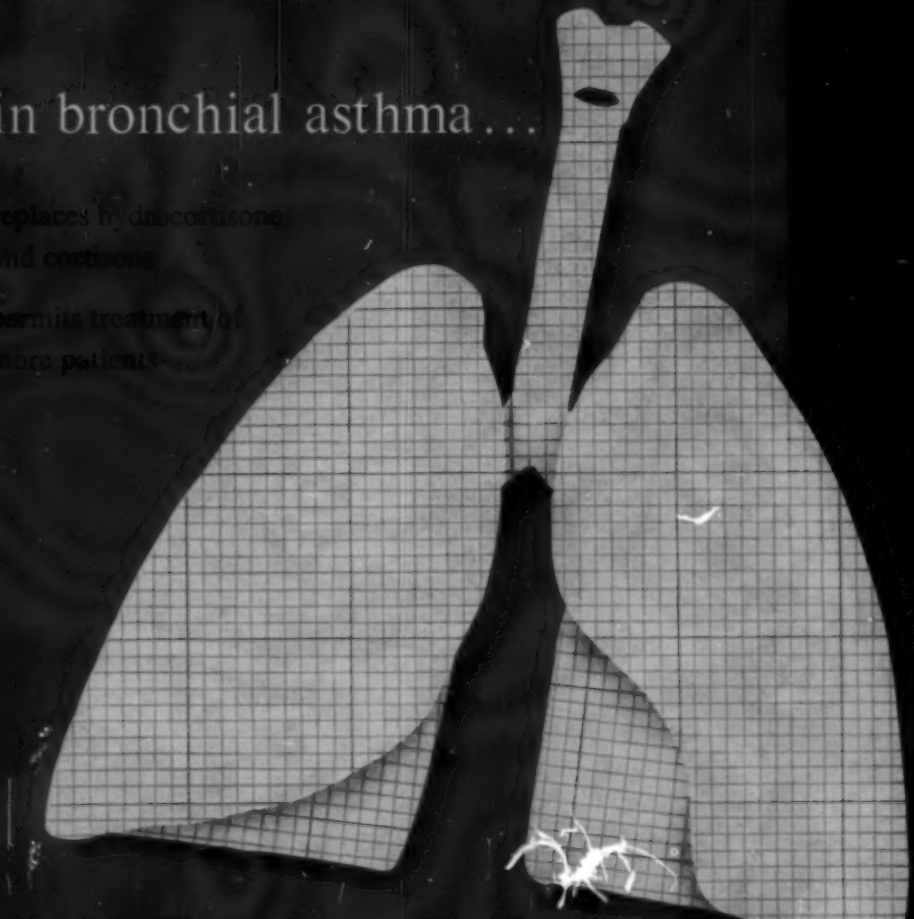

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